# Annual Review 2014

CHDR
Centre for Human Drug Research

# Long-term vision

# Drug development requires an eye for complexity

**More studies, but not just more of the same. This was the goal of CHDR's management when the new facility was planned, and according to CEO Prof. Dr Adam Cohen, much of this goal has been realised in the past year. 'Our vision has come to life.'**

'Modern-day medicines are developed using complex research in order to address complex biological problems,' says Cohen. 'The synthesis and formulation of these medicines is complex as well. So when it comes to evaluating these compounds, why not use sophisticated methodology as well? Why cling to an instrument like the Hamilton scale questionnaire for measuring depression? Still, that has been the standard approach. Until now.' Sitting at the top floor of the new building, we have the same view that study participants enjoy when they stay at CHDR. It's a good place to be, and it's one of the many factors behind CHDR's success. Another factor is the less-than-traditional view of its management: often a bit at odds with current fashion, but always with the interests of doctors, pharmaceutical companies, and patients in mind. In recent years, many of the contrarian views shared by Cohen and his colleagues – for example, question-driven drug design – have become more mainstream. Thus, a company that wants to develop a new antidepressant will likely do more than simply check items on the Hamilton scale. With increasing frequency, they contract CHDR to perform a study using more advanced measurements, including the NeuroCart or resting-state fMRI (see also page 17).

## Meeting place

'Back when we started CHDR some twenty-seven years ago, our approach was already to facilitate meetings between people. When we first talked with the architects when designing this new building, we made it clear that we wanted the building to serve as a meeting place first and foremost. They did an excellent job, designing a highly transparent, open building. And I believe our approach has worked. I also think this approach is even more important today than it was twenty-seven years ago. The new drugs that are developed today often act upon several biological systems, affecting multiple organs and addressing several therapeutic areas. So it is also important to approach people from different disciplines and help them connect with each other. In drug development, we also must meet with other interested parties, including the registration authorities, investors, and patient organisations. The more communication that takes place, the smoother and more effective the whole process becomes, which is sorely needed, as drug development has become so complex and expensive that it's a miracle it still happens at all.'

To illustrate the importance of meeting with various experts, Cohen refers to the development of fluorescent markers for use in image-guided surgery (see also page 27). Far off the traditional path of drug development, this new advance requires collaboration between pharmacologists, surgeons, basic researchers, and even mathematicians (who develop a model to predict the amount of fluorescent marker needed). Cohen: 'The sponsor for this study is an American company, and the product was developed in collaboration with Harvard University; so why would they want to conduct the first-in-human experiments in the Netherlands? I think it's because our culture facilitates – and even encourages – the meeting of minds. To me, when I see surgeons preparing for a study in our facility, I'm delighted, because it means that our vision has been realised.'

## Centralising patients

A recurrent problem in the early phase of drug research is finding the right patients – and sufficient numbers of these patients – to conduct a study. Until now, this usually required multicentre trials, in which each centre contributed a few patients. According to Cohen, there's an easier way. 'Instead of coordinating a study in 60 centres, where each hospital treats only three patients, we can recruit all 180 patients ourselves and do everything here. It's much more efficient to move the patients than to move the research. If a patient in Groningen wants to join our study, it saves us a lot of money if we pay his cab fare rather than asking a hospital in Groningen to join a multicentre study.'

In 2014, a psoriasis study conducted at CHDR showed that this approach works. In record time, sufficient numbers of patients were recruited, thanks to efficient collaboration with dermatologists and a direct advertising campaign. As the study's principal investigator Dr Robert Rissmann wrote in his blog at chdrblog.nl, the 'monocentre' approach reduces interobserver variance and makes the operational aspects much easier. 'And – most importantly – the patient experiences a professional, fully dedicated research atmosphere instead of a very busy outpatient clinic with long waiting times and bad coffee.'



## Trial@home

The next development will head in nearly the opposite direction. Instead of bringing patients to the research facility, CHDR plans to move part of the research into the patients' homes. Cohen points to his iPhone. 'Nearly everyone has one of these sophisticated pieces of technology in his/her pocket. But in drug research, we still work with paper booklets that people tend to lose or forget. Together with the BioScience Park company Cosine and Omnicomm (the company that acquired Promasys), we are now developing an application that generates apps. The first use of this application is a dermatology trial. It will provide a standardised way to take pictures of a skin lesion, which is very practical if you want to test the effects of a new dermatological compound. The app will also remind patients to apply the ointment, take a picture to document it, and send it straight to us. The data will automatically be filed here. It's a great way to both increase and confirm compliance.'

The next step will be to monitor subjects via their smartphones, using a simple adhesive sensor that measures variables such as skin temperature, movement, and even ECG. A Bluetooth connection will send the data directly to the patient's phone. Using these sensors in combination with apps that ask questions and may even monitor movement using the phone's built-in GPS tracker, useful data can be collected while the subjects go about their normal business. This provides a more realistic setting and allows us to recruit far more subjects than the conventional setup in which subjects must stay at our facility. As Cohen says, 'It eliminates the major reason to not be a test subject. If I ask you to stay here for the next two weeks, you will likely refuse. But if I ask you to come here just a few times, wear an adhesive sensor on your chest and just go home to your family, you are far more likely to participate.'

These sensors and apps will yield an enormous amount of data. So the next challenge will be to analyse all of this data. Cohen looks forward to the challenge. 'We will collaborate with researchers at Leiden University who are used to working with large datasets and with Cosine. For example, they provide the measurement systems for the European Space Agency; so they are not afraid of large datasets.'

Our conversation now returns to the theme of bringing together many disciplines, of providing a meeting place. As the clouds part and a bright beam of sunlight suddenly illuminates the Leiden University Medical Center and the BioScience Park, Cohen adds, 'Of course, we also invest in virtual meetings with students, colleagues in academia, pharmaceutical companies, and biotech companies around the world. We can bring people from just around the corner in touch with people in Sweden, the United States or Korea. That in itself can be highly gratifying, and it will also help solve scientific problems and advance our activities.'

# Increased turnover, more diverse activities, sponsored biomarker R&D

**In 2014, CHDR was busier than any other time in its history. According to CHDR's Chief Operating Officer, Dr Pierre Peeters, the recent growth in activities is the result of careful planning and a client-oriented strategy. 'We've always been good at science, and that's still one of our major strengths. But we've also invested in building strong relationships with our sponsors, and we strive to meet their needs in terms of swiftness and transparency. And I think we can do even more in the coming years.'**

## Record-breaking growth

The growth that started after CHDR moved to the new building in 2013 continued through 2014. In 2014, CHDR conducted a total of 39 studies comprising 1.084 subjects, a 46% increase from 2013. This impressive growth occurred at a time when the global economy was still recovering and pharmaceutical companies remained cautious regarding their investments. Peeters: 'To an outsider, this might look like magic, but to us, everything developed according to plan. Which makes sense, of course; after all, who builds a much larger facility to just keep doing the same amount of work?'

## Sponsored developments

A large part of the growth came from CHDR's long-term clients. Peeters: 'I always say that the most important element in business development is business maintenance. We actively invest in our relationships with sponsors anticipating their needs and evaluating each study thoroughly. We know what they are doing, and they know what we are developing.'

One of the ways to anticipate a sponsor's needs is to develop new biomarkers and other tools that will be relevant when new classes of drugs become available. These efforts at CHDR in terms of research and development can sometimes be sponsored by pharmaceutical companies. In the past year, several examples of this new collaboration model were realised. A new tool for measuring retinal blood flow in patients suffering from sickle cell anaemia; the validation of the PainCart; the development of a new method to study myelin synthesis in the brain; the creation of a library of resting-state fMRI 'signatures' of drugs in the brain – all of these fascinating new developments were sponsored by CHDR clients. Peeters: 'It is a win-win proposition. Sponsors benefit by using these sophisticated new tools to gather as much information as possible in the early stages of human drug development, and we can practise applied science while adding new methods to our own toolkit.'

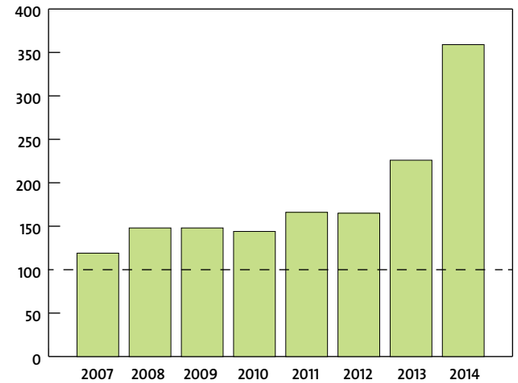
According to Peeters, another key aspect of business development is to 'make some noise'. He explains: 'If we validate a method or develop and calibrate a new instrument or biomarker, I think it's important to tell the world about it. The famous Dutch pharmacologist Everhardus Jacobus Ariëns used to say, 'Recognition does not come from sitting quietly in the corner.' So we use our website and other communication media to share new developments and present fact sheets and movies; and – of course – we attend conferences to discuss our work. In this way, we let our long-standing clients know that we're still active, and every now and then we attract new clients.'



## More patients

If we look at CHDR's activities in 2014 in more detail, it quickly becomes clear that in addition to increasing the volume of operations, CHDR also implemented several shifts in its activities. First-in-human studies with healthy volunteers still comprise the largest part of the work at CHDR, but the number of studies that involve patients has increased considerably. Peeters: 'At CHDR, we've always studied the effects of compounds in patients; but now in our new facility, it has become possible to accommodate larger numbers of patients for longer periods of time. We can also study the effects of several compounds using an outpatient approach. The various biomarkers and pharmacological approaches that we developed are ideally suited for early studies in patients, and the rewards are great – both scientifically and financially – if you can also perform the first studies in patients. I'm really glad that we are able to do that now.'

Contract revenues (relative to 2006)




## Further improvements

When asked about the immediate future, Peeters first stresses the importance of building upon success. 'We are not going to simply rest on our laurels, but we plan to keep the momentum going. There are still many ongoing developments, both scientifically and operationally. One aspect that always requires particular attention is data management. The core products that we deliver to our sponsors are the data and the report. These products must be flawless when we deliver them to our sponsors, as they will be used for their internal decision-making process and to apply for market authorisation. Both the FDA and the EMA require that the data be provided in the Clinical Data Interchange Standards Consortium (CDISC) format. Our data management software Promasys – which was developed at CHDR but is now owned by Omnicomm – still lacks the CDISC feature; so we need to send our data to another subcontractor for conversion. This feature will be added this year.'

Rapid growth in operations also poses a challenge to all staff members. Peeters: 'We've managed well so far, but in the coming year we will need more permanent employees for some positions in order to accommodate the growing number of studies and the increasing complexity of work at CHDR.'

# CNS research

# Imaging, functionality, and pharmacology of the brain combined

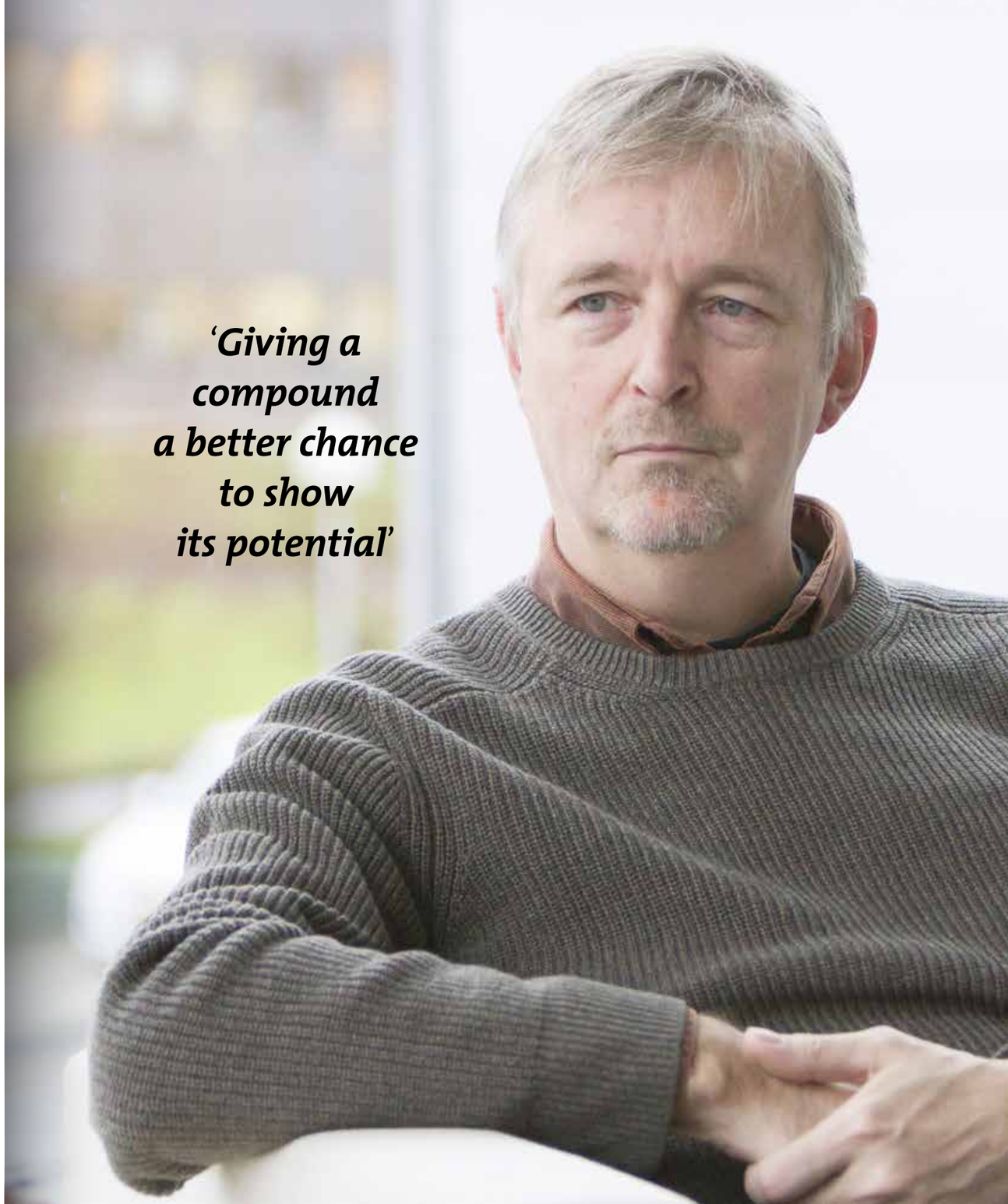
**The new CHDR facility offers researchers the possibility to study compounds both in healthy volunteers and in patients. 'We're off to a flying start, thanks to years of preparation,' says research director Prof. Dr Joop van Gerven. Van Gerven is responsible for studies in patients with depression and sleep disorders. A fascinating and powerful new tool for early drug development has been introduced: resting-state fMRI.**

## Combining technologies

The development of novel drugs for treating psychiatric disorders and other diseases of the central nervous system is both a promise realised and a challenge faced. There is currently a real – and growing – need for more effective therapies, and the number of potential targets can be dizzying. But the CNS is also the therapeutic area in which the highest number of drugs have failed. Van Gerven: 'It's not easy, but it can be made easier if basic researchers, pharmacologists, and clinical researchers are involved in all phases of clinical drug development. I'm convinced that in the past, effective compounds have been discarded in the clinical phase due to a lack of pharmacological information.'

Van Gerven draws a picture in which the classic path of bringing a drug to market authorisation – moving through the successive and isolated 'worlds' of basic research, pharmacology, and clinical research – is changing. A clinical pharmacologist who can translate a drug's basic mechanism of action into concrete tests of pharmacological activity – which are applicable in healthy volunteers as well as in patients – may help researchers design better clinical trials and may explain why some patients fail to respond to a given dosage.





'Thanks to several recent developments, these previously isolated worlds are now beginning to communicate better,' says van Gerven. 'Molecular biology has given basic researchers and clinicians a common language, providing a conceptual link between receptor biology and clinical effects. The more we know about how cells work, the better we can understand how drugs work. This underlying framework helps us better understand each other's view of the world, and it helps us collaborate more efficiently in each stage of the drug development process. For example, we applied basic knowledge regarding the physiology of pain into the development of our PainCart, a battery of tests that can measure the analgesic effects of drugs and can even distinguish between different classes of analgesics. And we can use NeuroCart – our battery of tests for the CNS – to investigate whether the effects of a single dose of a particular drug can predict the long-term efficacy of this drug in patients.'

Van Gerven and his colleagues have always advocated this integrated approach to drug development, so they are of course quite happy with the recent changes in the industry and in the regulatory bodies. They also invested heavily at a practical level, talking with fundamental researchers in academia, researchers at pharmaceutical companies, and clinicians. Three psychiatrists trained as clinical pharmacologists at CHDR. Now, two of these psychiatrists share the CHDR approach among their colleagues. The third, Dr Gabriel Jacobs, has now returned to CHDR to give a boost to drug studies in psychiatric patients. Jacobs is in close contact with both patients and psychiatrists, and his approach has already led to several successful early drug studies in patients with depression.

## TAKING CARE OF PATIENTS AT CHDR

For CHDR, having psychiatric patients as subjects called for some adjustments. Doctors, nurses, and test assistants received additional training to learn to care for patients with depression and other psychiatric illnesses. Some staff members were concerned that they would not be able to deal with any potential problems, but in practice everything worked out fine. Van Gerven: 'The patients who participated in our studies were well aware that the compounds they received would not cure their illness. There were here to contribute to the search for solutions in the future. And I think they appreciated the fact that they could talk in detail about their symptoms and about the changes they observed during the trial. The participation of these patients in early drug research is essential for developing new medicines.'



## An MRI signature of CNS compounds

In 2014, CHDR began to reap the rewards from its investment in a fascinating line of research that began years before: resting-state functional magnetic resonance imaging (rs-fMRI). This imaging technique enables researchers to visualise how a compound influences the overall functioning of the brain. fMRI works by measuring blood flow to various parts of the central nervous system. Most research uses this technique while giving the subject a specific task such as visual recognition or a mathematical equation. The changing patterns in blood flow to different regions in the brain offers a glimpse into the workings of our most mysterious organ. Resting-state fMRI works a little differently. The subject is not given a specific task, but is asked to simply relax and do nothing. Statistical analyses of the images obtained provide insight into the brain's connections in both health and disease. CHDR is one of the few institutes in the world that studies drugs this way. In collaboration with neuro-imaging experts at Leiden University Medical Centre, CHDR researchers have been studying the interaction between drugs and the brain. Van Gerven: 'We are building a library of patterns using well-known agents that act on the CNS, ranging from alcohol to neuroleptics. Now, we are reaching the stage where we can give subjects a new compound and see how its effects compare to our library of compounds. It's actually a statistical comparison, unlike an X-ray that I can hold up to the light; but we can find the specific signatures of CNS drugs in the images. We combine the information obtained from rs-fMRI scans with the results of our functional tests obtained using the NeuroCart. As we know from earlier studies, it can be difficult to distinguish functionally between compounds with similar general effects, for example alcohol and opiates. Imaging adds a whole new dimension to a drug's profile.'

The actual scanning is performed at the radiology facility at LUMC, where a dedicated 3T pharmaco-MRI scanner will be installed in the spring of 2015. This dedicated facility will enable researchers to conduct more efficient studies, with frequent measurements collected over longer periods of time and from more subjects. After the subject receives a test compound, several scans can be performed, revealing the compound's impact on the brain over time. The statistical analysis of these data – using tens of thousands of 'voxels' as the input – is highly complex and is not yet fully adapted to measuring drug effects. Therefore, novel analysis techniques are being developed in the United Kingdom at the University of Oxford's FMRIB Analysis Group. Van Gerven: 'Now that we have a dedicated scanner at LUMC and a growing library of drug signatures, we hope to advance the development of even more CNS drugs. I expect to see an increase in the number of candidate drugs in the coming years, as basic research points to interesting new approaches for treating depression, anxiety, and other psychiatric disorders.'

# Developing and testing new methodologies in brain and pain research

**A growing number of studies both in patients and in healthy volunteers, completion of two large studies in patients with Alzheimer's disease and small-fibre neuropathy, validation of the PainCart, and the development of radically new methodologies to study novel therapies for treating multiple sclerosis – one can say it's been quite a busy year for research director Dr Geert Jan Groeneveld and his team. 'As far as we are concerned, the economic crisis is really over.'**

## Emerging technologies

It's hard to overestimate the burden caused by neurological diseases such as multiple sclerosis, Alzheimer's disease, and ALS. This is no less true for various pain syndromes and painful disorders such as arthritis. And although we are still far from curing many of these conditions, several promising new drugs are in the pipeline. Despite many advances, successfully developing drugs that act on the central nervous system is notoriously complicated. Several hurdles must be cleared, including the inaccessibility of the CNS, the blood-brain barrier, and difficulty reliably measuring effects. Making comparisons with animal models can be difficult as well, given the obvious differences in brain size and function between animals and humans.

So this field – and perhaps even more than other fields – depends upon the use of methodologies that can adequately demonstrate target engagement. Groeneveld: 'First-in-human studies offer many unique opportunities to learn more about a new compound, its pharmacokinetics, and its effects on the human body. At CHDR, we specialise in seizing these opportunities, so that by the time we conclude a study, our sponsor has more than enough useful information to prepare the next phase of research, or to go back to the drawing board to iron out problems such as unexpected side-effects. This can save a sponsor – and its investors – millions of dollars down the road, and it can minimise the chance that subjects or patients will have serious complications.'

## Alzheimer's disease

'Ever since I started at CHDR, I have been interested in cognitive enhancement in Alzheimer's research,' says Groeneveld. 'We started with basic research on the cholinergic system. Soon, several compounds became available and needed testing. So we did quite a lot in this field, leading to our first PhD thesis in this area. We also established a fruitful collaboration with the Alzheimer Centre and the Alzheimer Research Centre at VU University Medical Centre (VUmc) in Amsterdam. Part of this collaborative research is performed in our dedicated clinical research unit at the neurology department at VUmc, where patients with Alzheimer's disease can participate in our studies.'

The next class of drugs being developed for patients with Alzheimer's disease includes monoclonal antibodies against the amyloid-beta protein, which is widely considered a cause ofthe disease. 'We were involved in a first-in-human study using such an antibody. It is a fascinating new development that might help slow the disease process or even prevent clinical manifestations. Of course, to be truly useful and effective, these treatments should be given in an early stage, preferably even before clinical symptoms emerge. Thus, together with the VUmc Alzheimer Centre, we will begin a study to measure cognition and markers of Alzheimer's disease in a large cohort of healthy elderly subjects. We will combine the CHDR's strength of recruiting large numbers of healthy subjects with the Alzheimer Centre's strength in studying Alzheimer's disease'.

## Multiple sclerosis

Also in collaboration with VUmc, CHDR is developing new strategies to test drugs for treating multiple sclerosis, a debilitating disease caused by loss of the isolating myelin sheath that surrounds neurons in the brain. The loss of myelin is caused by an inflammatory process, and until now, effective compounds against multiple sclerosis have focused on reducing this inflammation. However, a promising new approach is to stimulate the body's natural process of remyelination. This process occurs during the natural course of the disease as well, giving rise to the well-known erratic pattern of rapid function loss followed by a partial restoration of function. If a treatment can tip the scales in favour of restoration, this could immensely improve the patient's quality of life. But the challenge is determining how to study the potential effects of a completely new class of drug.

Groeneveld: 'We are currently developing several methods to measure the effects of these compounds. One such method is a clinical function test that will be performed in collaboration with ophthalmologists at VUmc. Using a high-speed camera, they can measure the movements of the eyeball as the patient looks from side-to-side. In many patients with multiple sclerosis, due to a loss of myelin in the brain nerves that coordinate eye movements the inward movement of the eye is slightly slower. So if a compound can indeed restore myelinisation, we can expect to see a change there, too. Best of all, this is a non-invasive measurement that will hopefully help us quantify the effectiveness of new compounds.'

To evaluate drugs that affect myelin synthesis and/or loss, CHDR is also developing another radically new approach that uses 'heavy water', in which the hydrogen atoms are replaced with deuterium ($D_2O$). Chemically, $D_2O$ behaves exactly like water, so the deuterium will be incorporated into various biological substances, including myelin and its degradation products. These degradation products can be measured easily in the cerebrospinal fluid. Groeneveld: 'We have already established the baseline in healthy volunteers. Now, we are well positioned to study compounds that affect myelin synthesis in patients and volunteers. We are doing this in collaboration with a biotechnology company. And we are developing mathematical models of myelin synthesis and degradation in order to estimate the rate of myelin formation using our measurements. We are now ready to use this information in our research.'

## Pain

Over the years, CHDR has developed the PainCart, a set of routine measurements used to test the effects of various analgesic compounds. Although the PainCart has proven its usefulness in practice, it had never been validated using a series of known analgesic compounds. Such validation is important for the study of new compounds, as it helps determine whether a possible new painkiller fits the expected profile. For example, if a new painkiller is expected to work like an opioid, the PainCart responses should match the profile of a subject who has received morphine or another opioid. Groeneveld: 'Everyone agreed that validation was important, but it never quite reached the top of our priority list. To do it right requires a substantial investment, and our budget for initiating our own research is always limited. So we were quite fortunate that we received a study grant from a large pharmaceutical company this year. We published our results, and we used the validated PainCart in several studies, including three studies performed on behalf of our sponsor. Now, we can show you precisely how your compound affects various types of pain.'

# Internal medicine, biomarkers and assays

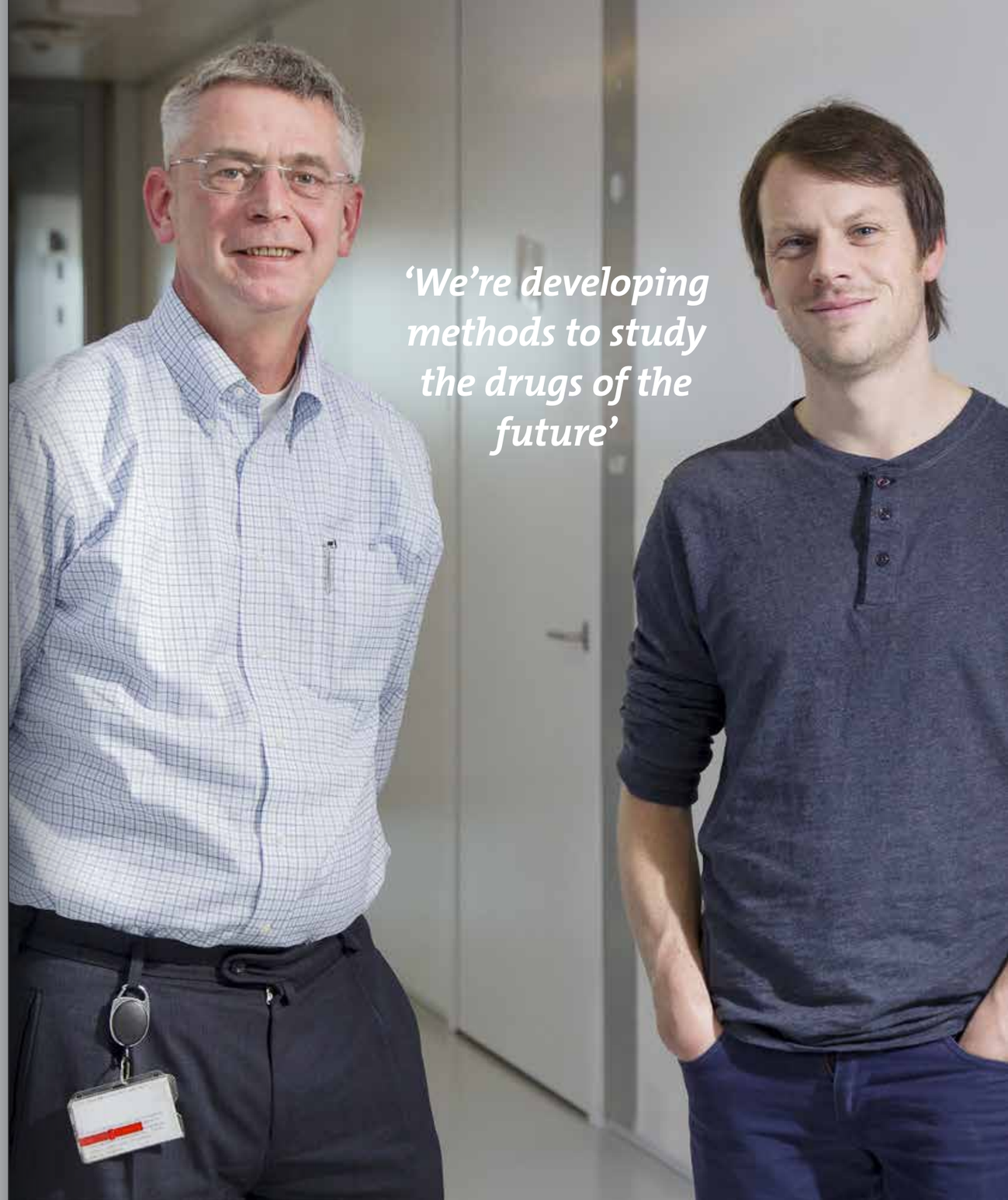
# Understanding the roots of health and disease to develop practical applications

**At the cutting edge between the laboratory and clinical applications, research directors Prof. Dr Koos Burggraaf and Dr Matthijs Moerland oversee a wide variety of studies ranging from biologicals to fluorescent markers for image-guided surgery, and from micro-dosing studies using labelled proteins, metals, and small molecules to the exploration of 'first-in-class drugs' in endocrinology.**

'Research is teamwork,' says Burggraaf. 'We do most of our studies together, and it's always a smooth collaboration.' Moerland explains how his background in basic biology helps him design a better study, to develop new biomarkers, and – of course – to communicate with other scientists: 'We can address such a broad range of subjects and therapeutic areas because we collaborate with clinicians and researchers from all around the world.' As a team, both Burggraaf and Moerland personify one of the core principles in CHDR's philosophy: early drug development requires an intensive interaction between preclinical science, pharmacology, clinical knowledge, and experience. The ability to communicate fluently between these disciplines requires both the ability to speak each other's language and a willingness to ask questions.

## Hunting for assays

'An important part of my job is to maintain contact with various groups that are developing assays and biomarkers,' says Moerland. 'If an assay looks promising, we will try to collaborate with that group. But of course, there can be a big difference between performing preclinical research and applying the results to human volunteers or patients.' Burggraaf agrees: 'Yes, the times when specialised assays could be performed almost as a hobby are long gone. These days, we need validated methods that can be GCLP [good clinical laboratory practice] certified. If you look in many laboratories today, you'll see assays that only work when "John" does it, but not when "Harry" or "Mary" runs the exact same assay. That might be tolerated in a scientific setting, but it's not suitable for our purposes.'



## A systemic view

To really understand how a candidate drug might work, you need more than just basic biological knowledge; you also need epidemiological information. Burggraaf: 'We need to know as much as we can about larger and more diverse populations in order to study the progression of a disease from the presymptomatic stage onward. What we eventually see in the clinic is often the result of a long-term process, the beginning of which often escapes our view. Who ever sees the very first stages of rheumatoid arthritis? Even a general physician will see a patient only after he/she has already been taking anti-inflammatory medication and painkillers for quite some time before finally visiting the doctor. The same is true for cardiovascular disease, Alzheimer's disease, and so on. I think we need to know more about the pathological cascades that ultimately lead to disease. In their early stages, there are probably many parallels between various pathologies. For example, a basic parameter such as body mass index is a risk factor for a wide range of conditions, from diabetes to cancer. So I think we need a more systemic view. Ultimately, this view will help us both identify drug targets and develop new ways to define the best endpoints for measuring drug efficacy.'

## Large molecules

Many of the new compounds currently being developed by academic and commercial researchers are complex biologicals such as monoclonal antibodies and recombinant proteins. Moerland: 'In the past year, we performed several studies using existing products. It turns out that these products have properties that are not sufficiently documented in the literature, and some of these properties can have consequences for clinical use. We have invested in this area in order to assist in the development and evaluation of novel large molecules.'

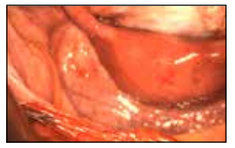
Burggraaf: 'If you ask the right questions, even so-called "routine" research suddenly becomes interesting. For example, consider biosimilarity studies, in which you compare a new compound with a known compound in order to see whether their pharmacokinetics and pharmacodynamics profiles match. It's a classic example of 'routine' research. But to us, it was an opportunity to study several interesting things. For example, we learned that the mechanism of cardiotoxicity in a particular cancer drug was actually a compensatory mechanism rather than true toxicity. Another observation that still intrigues us was noted by one of our students. He asked, "Why does the plasma level of some biologicals continue to rise even after you stop the infusion?" Moerland: 'The pharmacokinetics profiles of most biologicals are still poorly understood, and that's where we're making a real contribution. That's one of the reasons I love being a scientist at CHDR. We can answer questions that an academic laboratory cannot, because we have access to materials from sponsored studies. Another reason is that our findings can be applied directly to patient care. Of course, it's nice to publish a paper in a prestigious journal, but I like it even more when my work leads to better care.'



## Micro-dosing

With drugs that have complex pharmacokinetics profiles, predicting the optimal dosing and sampling schedule for a first-in-human trial can be difficult. To increase both the safety of our subjects and the reliability of the data, scientists at CHDR sometimes use a special method that they call micro-dosing. With micro-dosing, a tiny amount of the compound – far less than a normal starting dose – is labelled with an isotope for later detection; the compound is then given to the subject. Using either low-dose radioactivity or mass spectrometry, this labeled dose is used to measure the compound's pharmacokinetics. Moerland: 'Using these data, we can predict how the compound will behave in larger doses, and we can determine the optimum sampling schedule. We also used our micro-dosing approach in a government-sponsored study aimed at establishing the potential risk of metal exposure from deodorants.'

### Intra-operative fluorescence imaging



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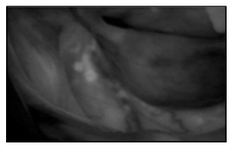

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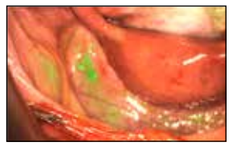

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## Getting surgeons back in touch

'A surgeon used to get a wealth of relevant information by seeing and touching the tissues during surgery,' says Burggraaf. 'Nowadays, with image-guided surgery and minimally invasive techniques, this tactile information is lost, and details can also be lost by reflections and movements. Last year, in collaboration with a US-based sponsor, we tested a new approach using fluorescent markers to selectively label specific tissues in both patients and volunteers. So in a sense, this new technology can give the surgeon a new sense of "being in touch" with the patient's tissues during the operation. It was an honour to work with surgeons and technicians in order to optimise this procedure. For me, this illustrates nicely how the field of clinical pharmacology is broadening even further.'

## CHDR Cardiology Services

In the coming years, CHDR will continue its fruitful interaction between innovative clinical pharmacologists and basic science researchers. In 2015, CHDR's expertise and collaborations in the field of cardiology will be formalised into what will be called CHDR Cardiology Services. Burggraaf: 'We have a long-standing tradition in cardiovascular research. We can now offer a one-stop shop to companies who want to evaluate the effects of a compound on several cardiac parameters, including the QT interval and other key electrophysiological parameters. This work is performed together with cardiologists at VUMC in Amsterdam, thus offering a broad scope of diagnostic procedures, including electrocardiography, cardiac MRI, PET and holters.' CHDR cardiology services will be led by Michiel Kemme MD PhD, a CHDR trained cardiologist-clinical pharmacologist and a staff member of the VUMC department of cardiology.

# Pharmacometrics

# Pharmacometrics: making optimum use of all available data

**The Pharmacometrics section at CHDR had a very busy 2014, developing new methods and models, writing standard operating procedures, moving their computing activities to a new server, and generally assisting with various new methods for clinical drug development within CHDR.**

'The transition from preclinical laboratory research to the first trials in human volunteers and first application in patients always poses many challenges,' says Jasper Stevens, CHDR's pharmacometrician. 'It's our job to gather as much relevant information as possible while minimising risk and discomfort for the subject. You have to build a strong bridge between the lab and the studies in humans. Pharmacometrics provides the tools to build this bridge.' Stevens explains how he uses all of the knowledge about a compound that was collected in preclinical research, with respect to both the action of the drug (pharmacodynamics) and the uptake and elimination of the compound (pharmacokinetics). Armed with this information, he then develops biological and statistical models to predict what will happen to a drug dose in the subject's body, and he compares these predictions with the actual data in a clinical study.

## Graphs, not points

Stevens: 'In addition to the classic approach in which you administer increasing doses to a volunteer and measure the drug's concentration in the blood at certain moments, you use these data to create and fine-tune a model – a graph – that provides highly educated guesses about what happens between those measurements. So by the end of the first stages in clinical drug development, you already have a fairly robust model to use in larger groups of patients, to optimise drug dose, and to check for variability in the drug's elimination profile. In these early stages, the model also helps you optimise the sampling times. And if for some reason you need take a sample at another time, you know how to adjust for this shift. With a classic statistical approach – where you have to compare two datasets – a delay in sampling can be problematic, for you cannot compare the value with anything. But if you compare *graphs* instead of just points, these data can make sense. This is particularly important in children, where of course their well-being is always more important than a study protocol; so you cannot always sample at the perfect time.'
According to Stevens, model-based statistics is fast becoming the new paradigm for evaluating the effects of drugs and their pharmacokinetics. Marked authorisation agencies such as the FDA and the EMA have installed pharmacometrics working groups in order to take full advantage of this new approach.
'A model contains much more information than the classic statistical approaches. So these agencies should welcome it, and they do.'

## New methods

The development and validation of new methods for use in early drug development is one of CHDR's core competencies. The Pharmacometrics section supports these efforts by developing a broad portfolio of techniques for analysing data. Stevens: 'For example, in diabetes research the focus has always been on insulin, glucose, and – more recently – glucagon. In most models, the number of glucagon receptors is assumed to be fixed; but of course, biologists know that this is not the case in real patients. The glucagon receptor can be overexpressed or underexpressed, and this can have serious consequences with respect to the treatment of diabetes. We are developing techniques to evaluate datasets including all relevant parameters, so we'll be ready when compounds that that act on the glucagon receptor are ready for testing in humans.'

Large molecules such as monoclonal antibodies also pose exciting challenges to pharmacometrics. For example, the translation of results from animal models to humans is more difficult, due in part to the complex pharmacokinetics profiles of these compounds. Large molecules can also trigger an immune response in patients, particularly if they are of non-human origin. Stevens explains the math behind comparing between a bovine protein and its recombinant human counterpart. 'Until now, our predictions have come true. So we are now advising a group of researchers who will perform the first-in-human comparison between the bovine and recombinant human proteins. We are developing better methodologies for analysing the pharmacokinetics and pharmacodynamics of these large molecules; many new drugs in a variety of fields fall into this category.'

New methods for sampling and analysing drugs and biomarkers can provide new views into pharmacokinetics and the underlying biological processes. A relatively simple example is the use of saliva to study pharmacokinetics. Stevens: 'Particularly in children, saliva sampling can be a viable, non-invasive alternative. We found that in adults, ninety minutes after dosing, the ratio between the dose and saliva concentration is stable. Until that time point, the results are not reliable in orally administered drugs. We did not do any studies in children yet, but we hope to do so in the future.' Pharmacometrics has also contributed to the development of new methodologies for use in multiple sclerosis and Alzheimer's disease research, for example by combining heavy water and measurements in cerebrospinal fluid (see also page 20).

## New computers

On a more operational level, the Pharmacometrics department has been working hard to write SOPs as part of the companywide quality assurance effort. 'In dealing with datasets, traceability is a key word for us. For example, if you re-format a dataset, perform calculations, etc., you must always be able to show the original data and where it came from. So we've scripted the entire process as a set of standard operating procedures.'

Another major effort was the move from stand-alone computers to a dedicated server. Stevens: 'Our calculations can be quite demanding in terms of processor use, so we might compromise the computing power of other systems if we use a shared server at CHDR. With our dedicated server, we are now ready for even more calculations, which is a good thing considering that both the number of subjects and the amount of data generated will only increase in the future.'

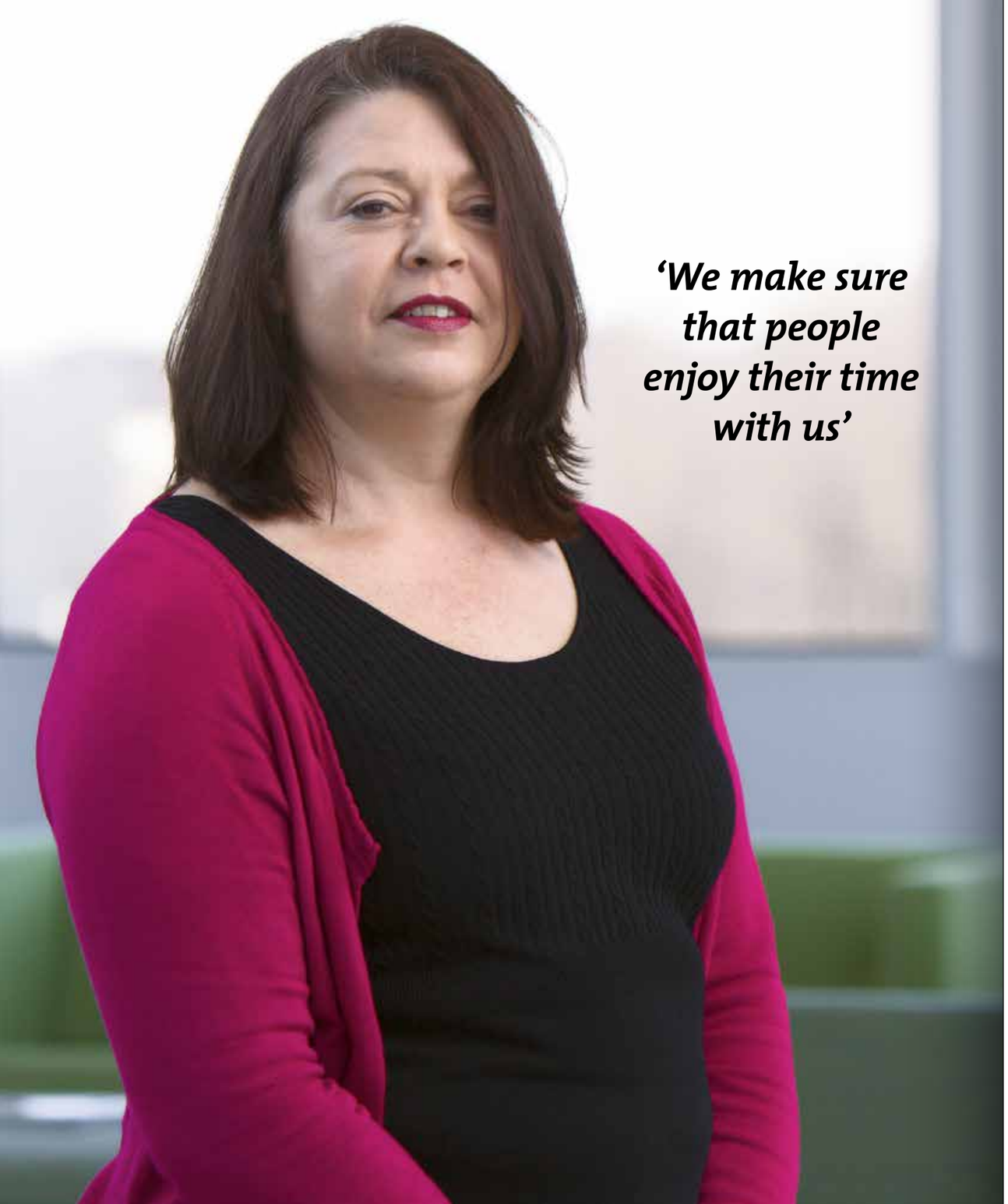
# Operations

## Accommodating growth in operations, increasing complexity, and longer trials

**As CHDR has grown in size, it has also grown in complexity. It's one thing to accommodate eight people for an 18-day stay; it's another thing entirely to coordinate an outpatient study with dozens of participants spanning nearly four months. Director of Clinical Operations Ria Kroon offers a glimpse at the inner workings of the CHDR machinery.**

### Overcoming logistical hurdles

'At CHDR, there's no such thing as routine,' explains Kroon. 'Each study is unique, and each time we need to juggle many factors in order to create the optimum conditions for our subjects, staff, and sponsor.' Her words illustrate how conducting a study with patients or healthy volunteers is like operating an intricate machine with many different moving parts. Her task begins when the contract is signed and the planning phase of a study starts. She summarises: 'First, we have to recruit subjects. Our recruitment department has many ways to attract volunteers and patients, including advertising in newspapers and online, and via patient organisations. When people come forward, we pre-screen candidates by telephone. In a special informational meeting, the candidates are told all of the ins and outs of the study, and they can then decide whether to participate or not. Next, the potential participants are screened by our nurses and doctors. You can imagine that at each step in the process, some people will drop out. And we cannot start the actual study until we've recruited enough subjects. We also have to make sure that we have enough personnel to care for all of the participants and to perform the necessary measurements. The logistics of sampling, data management, testing protocols, etc. – everything has to run smoothly and according to standard operating procedures. Often, we need to accommodate a sponsor who wants to run quality audits during their study. And of course, we always have more than one study running at the same time, with other studies in the planning stages.'



*‘We make sure that people enjoy their time with us’*

## Long stay

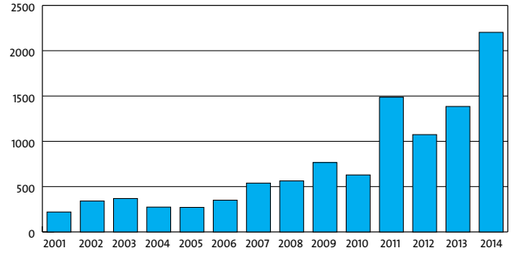
The high number of studies conducted in 2014 was one of the bigger challenges faced by the operational staff at CHDR, but Kroon explains that other changes at CHDR had consequences that were just as far-reaching. For example, she talks about the steep increase in the number of studies involving patients: ‘Working with patients always adds an extra layer of complexity. We need to hire nurses with specific experience in that field, for example psychiatry or diabetes. Another major change in our operations was the duration of the average stay at our facility. We were used to relatively short studies where subjects remained for just a few days. In 2014, we had one study in which eight people were required to stay in our facility for 18 days. That’s quite a long time to keep people inside. For me, the challenge was to keep them happy. We introduced more variety in the meals, and we organised different types of entertainment such as movies, table tennis, and video games on an Xbox. Even though they were surely happy to go outside again after the study, I’d like to think that they had quite a nice time here.’

Of course, most subjects do not stay that long. Some subjects can stay at home during a study, visiting CHDR on an outpatient basis. For example, this is standard in studies involving dermatological compounds. But for Kroon, this presents another challenge: ‘We have to check whether the participants returned already, and we need to remind them if they fail to come back in – in short, this type of study is as complex as in-house studies, but for other reasons. Regardless, in both situations, hospitality is our primary concern. Participants are always free to leave at any time. And of course, if they really want to leave the study, that’s okay. But I think it’s our job to make sure that they like it here, so they’ll have no reason to quit.’

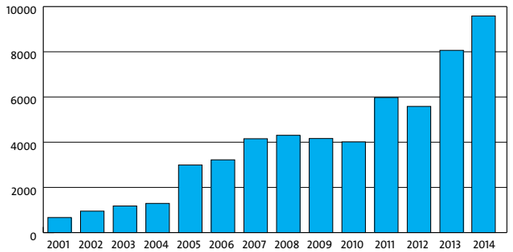
## Planning ahead

To make optimum use of the limited resources at CHDR, thorough planning is essential. From the moment a protocol is given the green light, Kroon and her colleagues start to plan ahead. ‘You read the protocol and talk to the study coordinator, asking what the specific challenges are in this study, what the minimal requirements are to start, and what problems can be expected. Shortly before starting the actual study, we do the same check with all personnel involved, particularly the nurses.’ In 2015, Kroon hopes to implement a new software package in order to make this task easier. After all, planning all of the clinical operations at CHDR is complex enough as it is.

### Number of volunteers, by year




### Total accommodation days, by year



# Quality assurance

# Internal and external audits keep CHDR quality at the highest level

**Both CHDR and its subcontractors have quality assurance systems in place in order to safeguard both the reliability of the data and the safety of all subjects and personnel. CHDR's Quality Assurance Manager Margreet Rienstra talks about her job and her continuing efforts to ensure high quality. 'The whole system must be in order. Each and every part of it.'**

'Quality assurance belongs to the entire organisation,' explains Rienstra. 'Financially, we are part of the overhead cost. But if we stop providing QA, we'd soon stop doing everything.' Rienstra is responsible for CHDR's quality system, which includes more than 200 standard operating procedures for internal audits and auditing subcontractors. She is also the primary contact for sponsors who conduct an external audit, which usually occurs during a sponsored study. 'I'm here to facilitate the work performed by many people. But I also have to remind everyone of the importance of following correct procedures. Being strict is part of my job. Everyone is aware of the importance of providing quality, but of course it can be a bit of a hassle as well.'

## Rules and regulations

Drug development is highly regulated, and a large part of the CHDR's Quality Assurance department's job is to follow these regulations. Good Clinical Practise (GCP) guidelines require that every relevant part of an operation will be performed in accordance with established Standard Operating Procedures (SOPs), and there must be records in place to prove it. GCP provides a certain degree of freedom in terms of how you can define your SOPs; but CHDR must also consider Dutch law and other regulations. 'Our sponsors want to be confident that the data we file can be used in the future to apply for market authorisation. So our SOPs must conform to the rules of the European Medicines Agency and the United States Food and Drug Administration. We must ensure that we continually update our SOPs to include the most recent guidelines from these agencies.' There can be other reasons to update an SOP – practical reasons, for example, or scientific developments. At minimum, all SOPs are reviewed every two years and updated as needed. Many SOPs are updated even more frequently, as rules or procedures can change at any time.

The SOPs in place at CHDR do more than merely describe the operational aspects of running a study; they also describe the statistical analysis of data and more general procedures, including what to do if things go wrong or if there is suspicion of fraud or misconduct. Rienstra explains that CHDR's SOPs are used internally to train personnel and to ensure that study activities are being performed are they should. They also serve to show sponsors how CHDR operates. A survey of all relevant SOPs is also part of both external and internal audits.

## Auditing

To ensure that everyday operations at CHDR and its subcontractors' sites are performed in accordance with these quality standards, both internal and external audits are performed on a regular basis. Each year, the Board of Directors chooses which processes will be audited from a list prepared by Rienstra. 'Auditing involves talking with people and watching how things are being done; but the main part involves checking the documents to confirm that everything is in full compliance with our standards. If I go to a subcontractor, I do the same thing. For new subcontractors, I may visit their site before we sign a contract. Sometimes, though, it's hard to get a clear picture if there are no data yet. In that case, we perform the audit during the study, taking samples of the results.'

External auditors – who want to ensure that CHDR complies with quality standards on behalf of the sponsors – face the same dilemma. Auditing beforehand may help confirm that their future business partner is legitimate, but an audit performed during the study can be much more informative. Rienstra sees a trend towards the latter. 'In the past year, we had eleven external audits, including one in the pharmacy at LUMC; this pharmacy is one of our most important subcontractors, as they prepare most of the pharmaceuticals that our subjects receive.'

## Future plans

The recent increase in the number of studies and overall turnover at CHDR has taken its toll on the Quality Assurance department as well. Until now, Rienstra has done the job on her own, with the occasional help of a freelance colleague. In 2015, she hopes to be joined by a colleague who will share the important role of providing quality assurance.
In the coming year, CHDR will also introduce an electronic learning management system to replace the authorisation records that have always been stored on paper. Rienstra: 'These authorisation records show us which SOPs you have been trained on. Of course, when you perform a procedure, everyone involved has to be trained and authorised. Electronic records are more practical because they are always up-to-date and you can access them whenever and wherever you need them. For this system, we are selecting the best supplier based on our quality standards. We need to be certain that the records will be available at the moment you need them; you don't want to have to wait because the system is down. Of course, we expect high quality from our subcontractors as well.'

| Audit type | Number of audits 2014 | Number of audits 2013 |
|---|---|---|
| Qualification / system audit | 5 | 9* |
| Study audit | 3 | 1 |
| Data management/statistics audit | 2 | 0 |
| Health, safety and environment audit | 1** | 0 |
| **Total number of audits** | **11** | **10** |

* *Includes 3 GMP audits conducted at the LUMC pharmacy*
** *Performed at the LUMC pharmacy*



# Educational mission

# Educating tomorrow's doctors and scientists

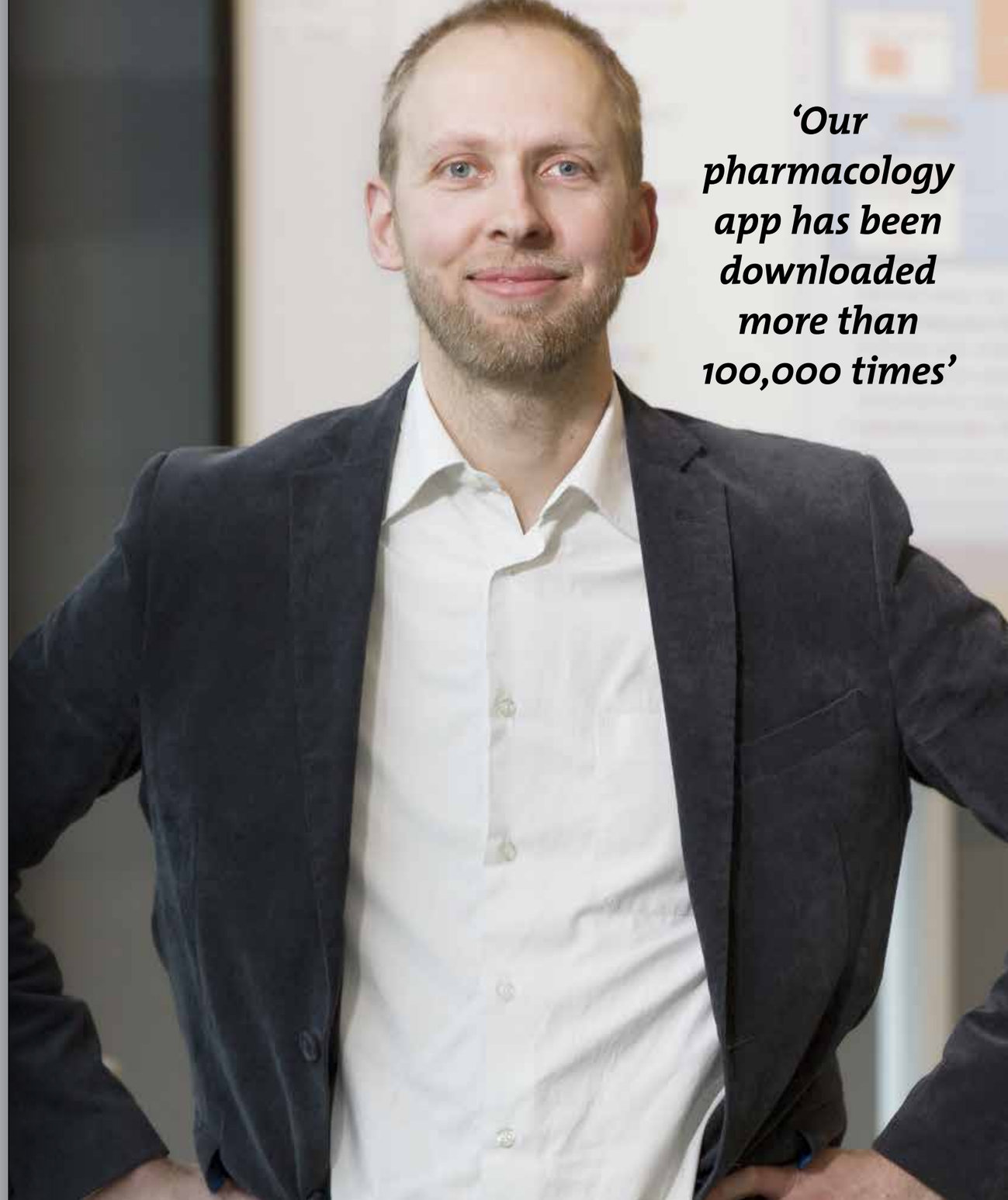
**In addition to their usual teaching roles at Leiden University and Leiden University Medical Centre, CHDR contributed to two new postgraduate courses to educate future biomedical entrepreneurs. And then, CHDR went on to teach the world. The Dutch viewing public can now enjoy 'vintage' lectures by Dr Adam Cohen via the online 'University of the Netherlands', and the Teaching Resource Centre's Pharmacology app has been downloaded on every continent. Dr Robert Rissmann, CHDR's Coordinator of Education, talks about these and other developments.**

## Educating future generations

Teaching others is not only fun; it's also essential. This has always been one of the core guiding principles in CHDR's philosophy. And it's a good thing, because CHDR staff members are active educators at Leiden University and LUMC. Our staff contribute to the curriculaof medicine, biomedical sciences, and bio-pharmaceutical sciences. For future doctors, it is of course highly important that they become fluent in applying pharmacological principles to clinical problems. Rissmann: 'Like other medical schools in the Netherlands, we use the Guide to Good Prescribing, a WHO-approved six-step model to help medical students apply these principles systematically. After a few years of practise, the complex process of prescribing a drug using a rational approach becomes automatic, just as learning to drive a car requires active step-by-step thinking that evolves into a set of automatic movements after a while.' In biomedical sciences and bio-pharmaceutical sciences, the focus is more on clinical drug research and on understanding the interactions between drugs and diseases.

### LEIDEN FUTURELAB

In the summer of 2014, CHDR contributed to two new post-graduate courses under the umbrella of Leiden Futurelab (leidenfuturelab) . To quote their website, the aim of this learning centre is to produce 'physician-researchers and biomedical scientists who have an entrepreneurial spirit'. Rissmann: 'The course that we hosted covered modern clinical development and clinical trials. The participants learned to prepare a clinical development plan, including risk analysis for a medicinal product utilising available preclinical data. In the end, they wrote a clinical trial application. The other course focused on intellectual property in high-tech start-ups. IP is the main capital for a fledgling company, so it's extremely important for them to know how to manage their IP. Both of these courses received outstanding evaluations, and an entire post-graduate curriculum for researchers and clinical scientists is now being developed.'



## Resources

Like any other human activity, university education has its own trends and fashions. A few years ago, the thinking was that acquiring knowledge is essentially useless, as it becomes obsolete so quickly, and students should learn *where* and *how* to find the information they need. But according to Rissmann, this trend is reversing: 'Some knowledge – such as a basic understanding of the underlying physiology and the targets of common drugs – is essential to understanding and integrating information and using it in practise. So we think students should acquire that basic knowledge as a necessary foundation. In pharmacology, things change as new mechanisms are discovered, but there remains a core body of knowledge that is worth committing to memory.'

Of course, the pendulum doesn't have to swing back all the way. Medical education will likely never again be as it was decades ago, with mostly large-scale lectures given in an auditorium crammed with 200 students or more. Rissmann: 'We increasingly believe in a blended learning strategy. Students learn the basics online, in web-based lectures and other online resources. We then get together with the students in relatively small working groups, where we can focus on applying the knowledge they've accumulated. With this approach, you make optimal use of the hours we have together with our students. But of course, this approach requires high-quality online content. We therefore use the P-scribe e-learning environment for medicine and pharmacy students in the Netherlands and Belgium. With our own set of online resources, the Teaching Resource Centre (TRC), we are investing in new graphics using 3D animations. Much of this has already been implemented in the TRC app, which can be downloaded for free to Apple and Android devices.

This year, we reached an important milestone: one hundred thousand downloads worldwide (Education/trc). To me, that's one of the highlights of our work. It won't earn us a penny, but it's good to know that future doctors all over the world – even in developing countries – can benefit from our knowledge.' The contents of the app were developed from years of CHDR's pharmacology education. The app itself was programmed by Hans Pinckaers, an enthusiastic and creative medical student who developed this mobile pharmacology resource.

Connected to the TRC is the P-scribe platform, which can be used for self-study as well as to generate exams. According to Rissmann, the platform offers many advantages to the teachers as well. 'We offer sample exams, which show us exactly where there are gaps in the students' knowledge, so we can focus on closing those gaps when we see our students again.'



## Pre-university and post-graduate students

In addition to teaching university students, CHDR also contributes to several other educational programmes. Some of these are aimed at bright high school students and even the Dutch general public, for example the 'University of the Netherlands' lectures. Rissmann: 'We believe it's important to show future students how interesting clinical pharmacology and clinical drug development can be. It provides them with an attractive option to consider for their future career.' At the other end of the spectrum are internships for future scientists both from the Netherlands and from abroad. At any given time, several students can be found learning about clinical drug development at CHDR. Post-graduates can also join the research efforts, for example as a PhD student. In 2014, three PhD students at CHDR defended their theses.

At CHDR, pharmacologists and clinicians with a special interest in pharmacotherapy and clinical studies can train to become a clinical pharmacologist. This special training programme can be completed in one year full-time, or it can be spread out over several years. The curriculum includes courses and practical training in how to conduct pharmacological studies in healthy volunteers and patients, and it can include clinical work, for example advising doctors regarding the choice, dosage, adverse effects, and interactions of drugs. These skills are becomeing increasingly important as the complexity of pharmacotherapy increases, particularly in university hospitals. Of course, many clinical pharmacologists are actively involved in clinical drug development, either in an academic or healthcare setting or at a pharmaceutical company.

### WEBLINKS

MedicalEducation.nl

Download the TRC app here

leidenfuturelab

Pscribe

Universiteit van Nederland
(in Dutch, first of several lectures)

# Scientific review

# The Scientific Advisory Board discusses every protocol

**CHDR's Scientific Advisory Board meets monthly, and their primary task is to analyse the scientific merits of a protocol before it is sent to the Ethics Committee. The Board also reserves time to discuss questions from project leaders and interns. 'It's a rare opportunity to learn from experts in their field,' says senior clinical scientist Dr Ingrid de Visser, who is scientific secretary to the SAB.**

## Checks and balances

Ensuring high scientific quality in drug development is critical at CHDR, not only to ensure that the sponsors get the right answers to their questions, but also as an ethical responsibility to the volunteers and patients who participate in each study. Subjects contribute their time and assume the risks, so it's only natural that the study's design should help answer the questions it was designed to answer. Therefore, as an extra check of scientific quality, each protocol must pass a critical test: review by the Scientific Advisory Board (SAB). De Visser explains: 'Of course, as clinical scientists we will make sure that our approach is state-of-the-art. But because we are also involved in cutting-edge research, it's just good practice to have a panel of experts check every detail. Otherwise, you might overlook a critical detail.'

## Early discussion

As the name implies, the Scientific Advisory Board does not decide whether a study will move forward or not. But their advice will play a large role in the final decision by the Scientific Review Committee (which is composed of the research directors and senior project leaders) whether to apply for approval from the Ethics Committee or not. De Visser explains: 'If we send a protocol to the Ethics Committee despite a negative recommendation, they might also reject it, possibly for the same reasons. But of course, it can be problematic if a protocol receives a negative recommendation at a relatively late stage. Therefore, we try to consult the SAB as early in the process as possible. If the protocol needs revising, we'll have more time to discuss it with the sponsor.'

The SAB also contributes to the education of clinical pharmacologists and interns. De Visser: 'SAB meetings have always been open to everyone at CHDR, and many project leaders, interns, and others use this opportunity to see how protocols are reviewed and discussed. But to strengthen the educational aspects of our SAB meetings, we now start each meeting by discussing questions from project leaders and interns. The Chairman actively invites them to come forward with their questions and comments. After this discussion, the members will then state their opinions regarding the protocols.'

In 2014, the SAB met every month, to review the increasing number of protocols prepared by CHDR staff. De Visser: 'All SAB members always try to attend every meeting. Of course, sometimes they have other duties, and sometimes the protocols to be reviewed are quite far removed from their own discipline. So I always admire their dedication to the SAB.'

For the project leader whose scientific protocol is being discussed and scrutinised, an SAB meeting can be a source of stress. But they usually welcome it because they also know that it will help strengthen their scientific prowess. Overall, CHDR is doing well when it comes to its scientific productivity, both quantitatively and qualitatively. As the CWTS wrote in the 2014 evaluation of CHDR's scientific output: 'As CHDR currently publishes in better cited journals, this may improve the visibility of CHDR's research output.' In 2014, CWTS again analysed CHDR's output; this report will be presented to the SAB in 2015.

De Visser: 'Doing your PhD research here is a good way to broaden your views of science and the process of drug discovery. You will get to participate in studies in fields other than your own, increasing your clinical research skills. I know from experience how useful that is, and what a unique opportunity it represents. I did my PhD work here, did some other things after that, and then I was fortunate to return to CHDR.'



# Human resources

# Taking care of more than 250 people

**Hiring dozens of people may not sound easy, but to veteran Human Resources Manager Margreet ten Kate, it is. The informal atmosphere at CHDR and the organisation's transparency contribute to creating a fluid process. 'I see many people in staff positions who first came here as a trainee or test assistant back when they were still students.'**

'I've watched CHDR grow from the very beginning,' says Ten Kate. 'I used to say, "When we have more than 50 people here, I'll be gone." Today, we have more than 250 people on the payroll, I'm still here, and I still like it. Somehow, we've managed to keep the best qualities of a small-scale organisation alive, despite our growth. CHDR still has an open atmosphere, and everyone is very accessible.' In the early days, Ten Kate had a wide variety of responsibilities, including purchasing office supplies, doing administrative work, and paying the bills. Gradually, many of these tasks dropped away and she focused on human resources management. 'I developed my own system, using my own pragmatic approach. Recently, when I wanted to take an extended leave, I had to document all of my responsibilities so someone could take over temporarily. This was quite a job, but it was also satisfying to see how all of my daily routines add up to something useful.'

## Turnover

At CHDR, the need for personnel depends largely on the number of studies being performed at a given time. To meet this highly flexible demand, a large number of people are on call, including test assistants and some of the nursing staff. Ten Kate: 'Turnover is generally high among these temporary employees and on-call staff. For example, medical students become interns and no longer have time for us, nurses move on to other jobs, and so forth. On the other hand, we have an extremely low turnover rate in staff positions, so the faces on our website rarely change. That's because people really like it here, and if you fit in, you'll find a niche where you can develop yourself even more. That's one of the things I like about CHDR: to see how people come here, maybe go somewhere else, then return and often stay for many years in a staff position.'

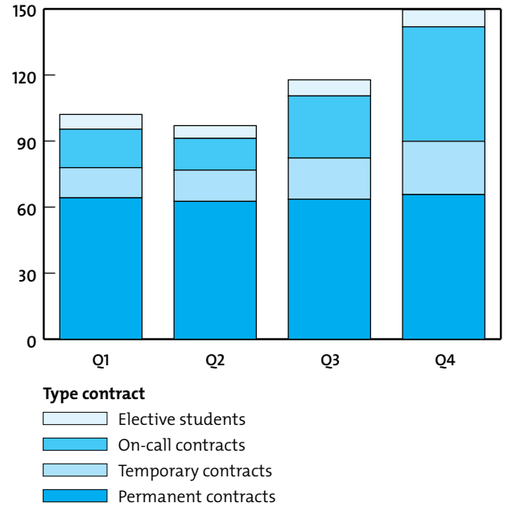
Hiring a new employee rarely takes Ten Kate more than half an hour, even for new hires from abroad. ' If you have a BSN – the Dutch social security number – it's easy. Sometimes, though, I have to arrange everything with the authorities, for example when a new employee comes from another country. If someone comes from far away, I will even help him/her find a place to live. In many ways, it's become a little easier to hire people from outside the European Union, particularly for the highly specialised jobs that we offer. We always have a large number of people from all around the world who come here for an internship, for PhD research, or as a postdoctoral fellow. So many nationalities are represented here.'

## Applications

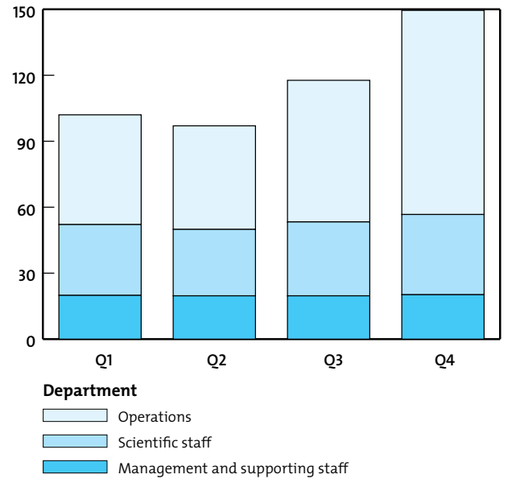
Ten Kate frequently receives open applications for jobs at CHDR. 'If it's a serious enquiry, including a résumé, I will reply within a day. I think people have the right to know what I do with their letter. I also receive many emails from people who clearly have no idea how to apply for a job; they don't put any effort into visiting our website to see what we do. Every once in a while, I take the time to explain to them that this is not how things work. Call it my motherly contribution to their career.'

Staff and personnel at CHDR can always come to Ten Kate with a question. 'People walk into my office quite regularly, with many different questions. As I said, we have a very open organisation. That's part of the job, and I love it. But sometimes it can be a bit of a distraction, too,' she adds with a smile.

**Summary of contracts, 2014**




**Summary of department members, 2014**



# Appendices

# Governing bodies

## Management Team

**Chief Executive Officer**
- Prof. Dr Adam Cohen

**Chief Operations Officer**
- Dr Pierre Peeters

**Research Directors**
- Prof. Dr Joop van Gerven
- Prof. Dr Koos Burggraaf
- Dr Geert Jan Groeneveld
- Dr Matthijs Moerland

**Director of Clinical Operations**
- Ria Koon

**Financial Director**
- Bart Mooy, Msc RA

## Scientific Advisory Board

**Chair**
- Prof. Dr Piet Hein van der Graaf

**Members**
- Dr Bart van Berckel
- Dr Bert de Boer
- Prof. Dr Meindert Danhof
- Prof. Dr Thomas Hankemeier
- Prof. Dr Tom Huizinga
- Prof. Dr Ron Kloet
- Prof. Dr Cees Kluft
- Dr Karen Malone
- Prof. Dr Cees Melief
- Dr Ram Sukhai
- Dr Noortje Swart
- Prof. Dr Christian Taube
- Prof. Dr Frans Zitman

## Supervisory Board

**Chair**
- Frans Eelkman Rooda, Msc MBA
  *(appointed June 23, 2014)*
- Martijn van der Mandele, PhD MBA
  *(served full-term until June 23, 2014)*

**Members**
- Willem te Beest, Msc
  *(served until November 18, 2014)*
- Dr Bernard Cohen
- Dr Jan Hendrik Egberts
- Dr Peter Leijh *(vice-chair)*
- Prof. Dr Marcel Levi

# Bibliometric analysis

**As in previous years, CHDR performed a comprehensive bibliometric analysis for 2014.**

This analysis enables us to evaluate CHDR's publication performance and compare our performance with previous years. Furthermore, it helps evaluate the impact of CHDR's research, and it provides a powerful tool for comparing CHDR's performance with the performance of benchmark institutes.There are many research activities that can be counted, but the most basic and common is the number of journal publications, which may act as a measure of research output. Please note that the annual numbers of publications can only be concluded in the course of the following year and therefore the research output up until 2013 is provided.

## Publication output

Many research activities can be quantified; however, the most basic and commonly measured output is the number of publications. It is important to note that the final numbers of publications in a given year can only be determined in the course of the following year; therefore, research output is provided through the end of 2013.

Table 1 Benchmark institutes

| | |
|---|---|
| PRA, Neth | PRA international, Zuid-Laren, the Netherlands |
| Edinburgh | BHF Centre for Cardiovascular Science, Edinburgh: Pharmacology, Toxicology & Therapeutics |
| Heidelberg | Heidelberg: Clinical pharmacology and pharmacoepidemiology |
| LUMC | LUMC: clinical pharmacy and toxicology |
| Radboud | Nijmegen St Radboud: Pharmacology and Toxicology |
| UMCG | UMCG: clinical pharmacology |

Figure 1 Number of publications by CHDR, by year

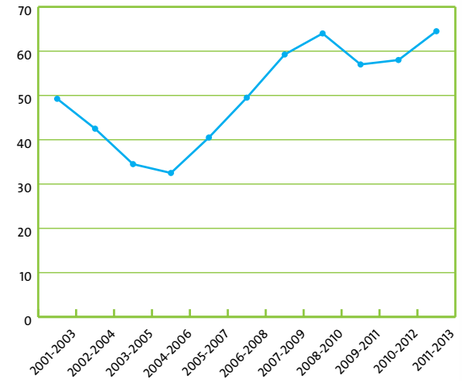



Figure 2 Publications by CHDR and benchmark institutes, by year

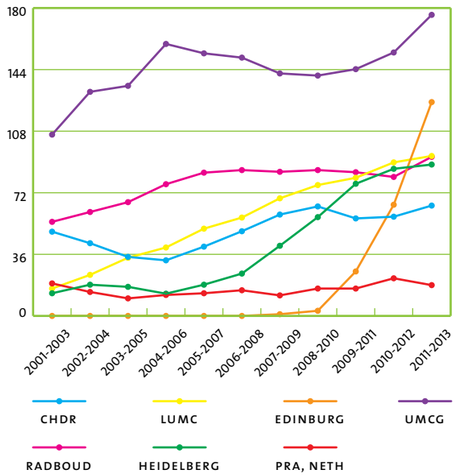
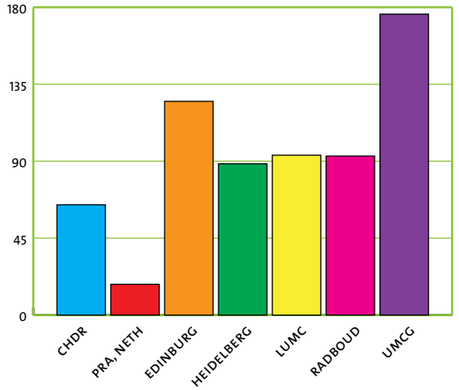



Figure 3 Publications by CHDR and benchmark institutes, 2011-2013




CHDR's publication output in the last complete 3-year period (2011-2013) increased compared to the previous period (2010-2012). This increased number of publications is a clear reflection of CHDR's growth; each year, CHDR performs more clinical studies than in the previous year. Importantly, CHDR's publication output is on par with the output of most university benchmarks. Although measuring just the absolute number of papers published can help us compare CHDR's output with other institutions, the number of researchers at each institution is also a factor. Thus, given that the number of researchers varies among benchmarks, comparing the *impact* of the publications may be more appropriate.

Table 3 Publication indicators

| Indicator | Dimension | Definition |
|---|---|---|
| MNCS | Impact | Average normalised number of citation of the publications |
| MNJS | Journal impact | Average normalised citation score of the journals in which a research unit has published |

## Citation impact

Citations are included in publications to provide a frame of reference so that readers can find additional and/or supporting information – for example, a more detailed description of methods or previously published studies that support the current results. Tracking citations is a commonly used means to evaluate the short- and long-term impact and effect of published research. The Mean Normalised Citation Score (MNCS) is often used to measure an institute's citation impact. MNCS reports the normalised impact of research published over a 4-year period (excluding self-citations). Thus, MNCS provides an objective, normalised tool for assessing CHDR's research performance and comparing that performance with previous years and with other research institutes.

To evaluate the citation impact of an institute's body of publications, MNCS must be measured at least one year after the issue date. Thus, we measured citation impact through 2013. A normalised citation score of 1.0 indicates that the number of citations matches the average number of publications in the field.

**Figure 5 Citation impact trend of CHDR and benchmark institutes, by year**

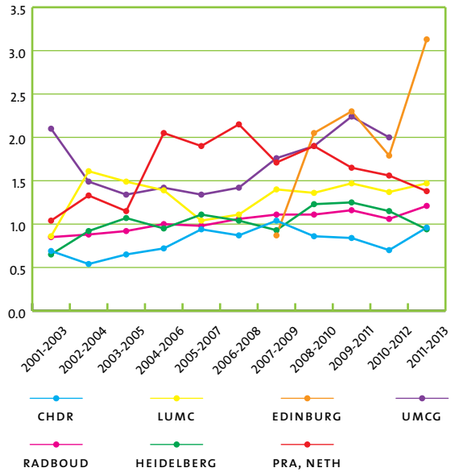
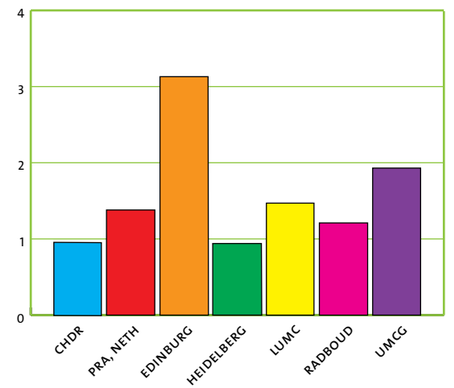



**Figure 4 CHDR's citation impact, by year**


**Figure 6 Citation impact of CHDR and benchmark institutes, 2011-2013**






CHDR's citation impact has increased steadily since 2010 and is currently on par with the global average (0.96). CHDR's citation impact is also on par with pharmacology and clinical pharmacology departments at Radboud University and Heidelberg, two of our benchmark institutes.

On the other hand, three other benchmark institutes – Edinburgh, UMCG, and PRA, the Netherlands – have higher impact scores than CHDR. However, their high citation scores are due primarily to a relatively small number of publications that have been cited many times (for example, one publication was cited more than 3000).

## Journal impact

The Mean Normalised Journal Score (MNJS) provides a method for measuring the impact of a scientific journal. Generally, MNJS is used to measure the relative importance of a given journal within its field; journals with a high impact factor are considered to have a larger impact on the field than journals with a low impact factor.

Although CHDR's current MNJS (for 2011-2013) is slightly lower than in the previous period (2010-2012), it is similar to the MNJS of most of our benchmark institutes. Moreover, CHDR's journal impact is higher than its citation impact, meaning that CHDR tends to publish in journals that attract more citations than our own publications.

**Figure 7 Bubble plot of citation impact for CHDR and benchmark institutes as a percentage of entire oeuvre (*x*-axis) and the number of citation (*y*-axis), 2001-2013**

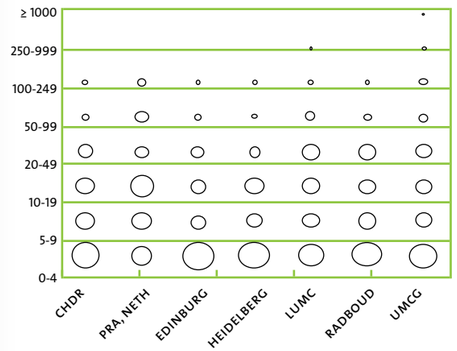



**Figure 8 Journal citation impact trend of CHDR, by year**

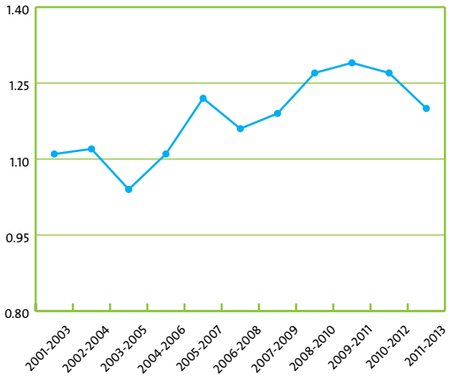


Figure 9 Journal citation impact trend of CHDR and benchmark institutes, by year

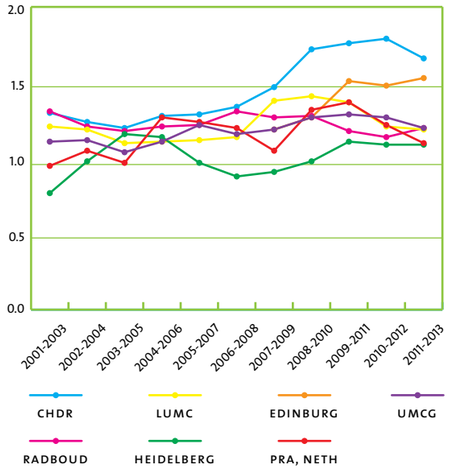
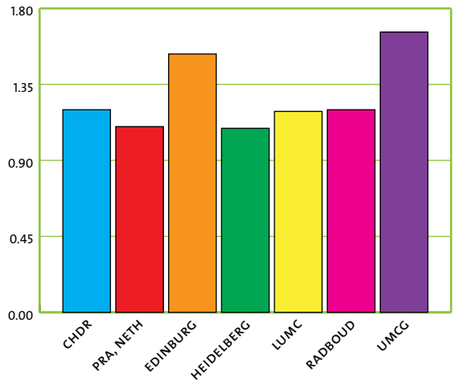



Figure 10 Journal citation impact of CHDR and benchmark institutes, 2011-2013




## Conclusions

CHDR's recent growth is reflected in CHDR's growing research output: indeed, CHDR's research output has been increasing steadily and is now on par with the global average. In addition to publishing more papers, the impact scores of these publications have also increased. Finally, CHDR continues to grow, introducing new technologies and establishing new collaborations and partnerships.



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