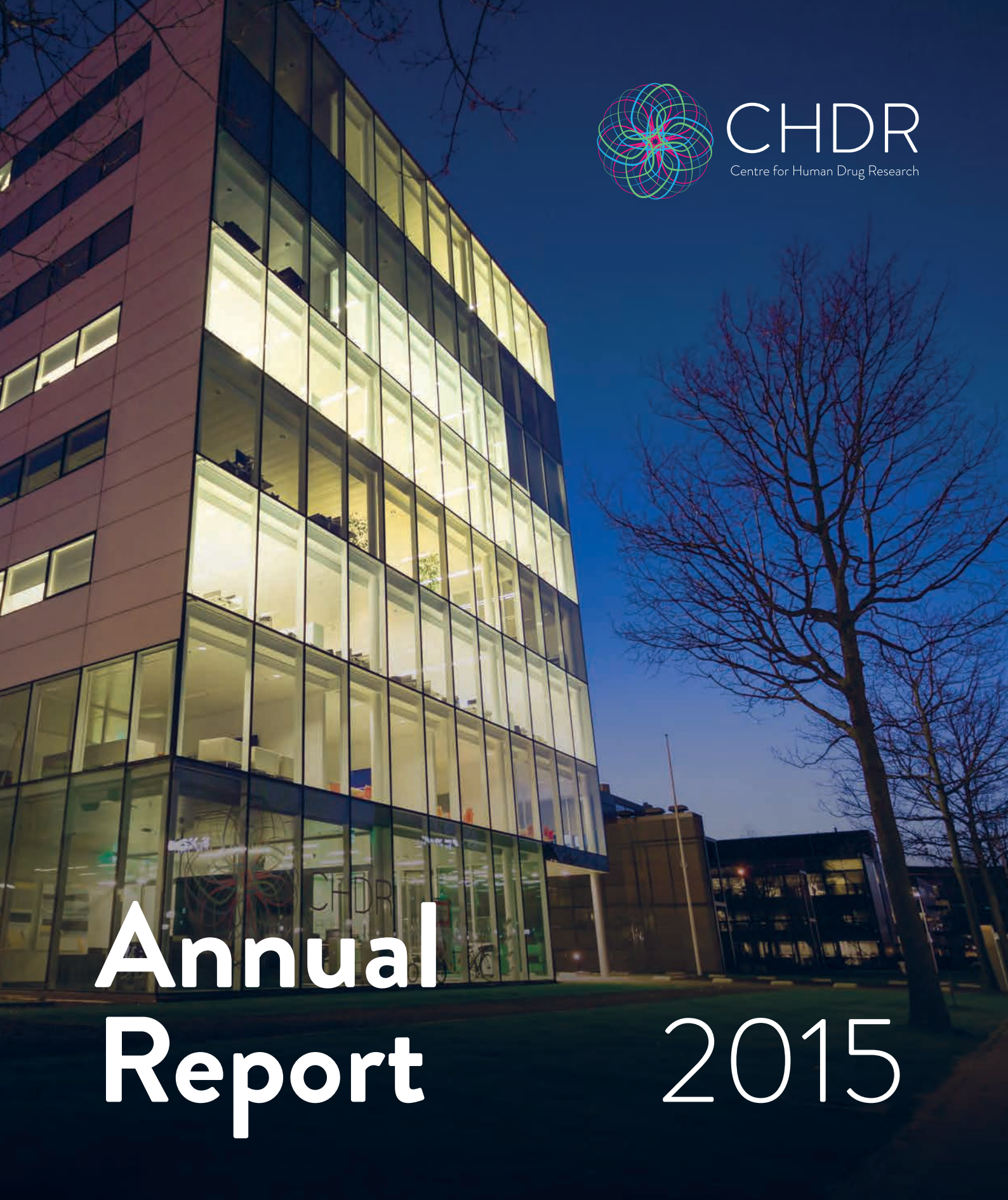

CHDR
Centre for Human Drug Research
Annual Report 2015

Word from the CEO

In 1987, we conducted our first experiments in a temporary building with a staff of four and under conditions that would certainly raise eyebrows today (but were considered best practice at the time). From that humble beginning, CHDR has come a long way, and this annual report reflects that growth.

CHDR is one of only a few CROs in the world that have maintained a solid - and growing - position. For the third consecutive year, our total revenues have grown significantly, and CHDR now enjoys a healthy financial position (see Table). In addition, our net cash flow has allowed us to establish a well-funded continuity reserve, providing sufficient resilience to face the challenges ahead.

	2014	2015
Solvency ratio	**37%**	**50%**
DSCR	**6.9%**	**12.2%**
Current ratio	**1.5%**	**2.6%**

DSCR, debt service coverage ratio

Our profit margins allow us to maintain a sizeable R&D budget, representing approximately 10% of our turnover. By continuously developing new R&D programmes - often in collaboration with industrial partners and/or academia - we can remain at the leading edge of modern drug development, ensuring that we're the best possible CRO for sponsors.

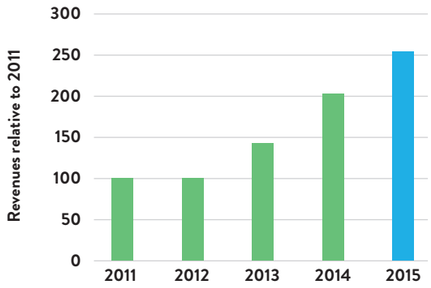
Of course, an annual report is a good way to reflect on past performance, but it's also a great opportunity to look ahead. Our strong financial position will allow us to expand in several areas in the coming years. Patient studies comprise an increasing percentage of our work, and our recruitment success continues to exceed all expectations. We are also continuing to expand our capacity to develop innovative methodologies, including novel imaging techniques, functional tests, and translational biomarkers. As our patient studies expand, the need for home monitoring also increases, and we are developing cutting-edge devices and software to meet this need.
Last - but certainly not least - individual medicinal compounds are becoming increasingly rare, and we are prepared to work with drug-drug, drug-device, and drug-nutrition combinations.

Achieving this high level of continued success is possible only with a strong network, and CHDR has established partnerships with both the Leiden BioScience Park and Medical Delta. These partnerships will help ensure that CHDR remains at the forefront of innovative drug development and clinical research for the next 30 years. These long-lasting collaborations are the embodiment of an old African proverb: 'If you want to go fast, go alone. If you want to go far, go together.'

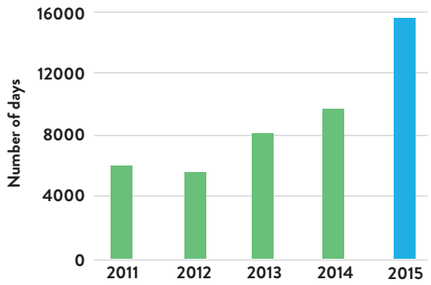
Contents

CHDR at a glance

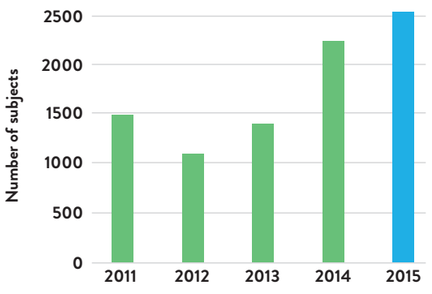
Contract revenue



Accomodation days



Subjects screened



2015 at a glance

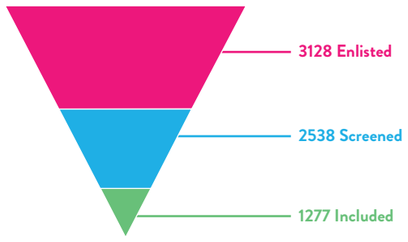
53 studies

36 contracts signed

27 articles published

>40,000 volunteers available

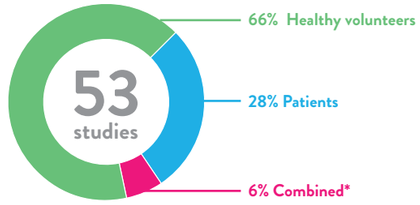
Subjects recruited



Overall client satisfaction

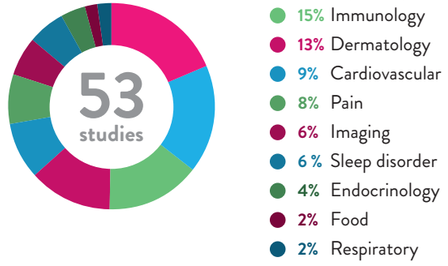
8.6

Studies with healthy volunteers and/or patients

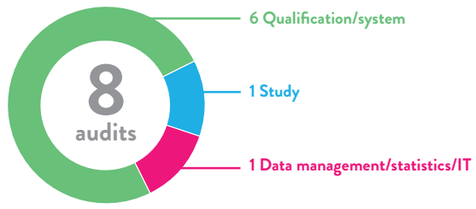


*both healthy volunteers and patients

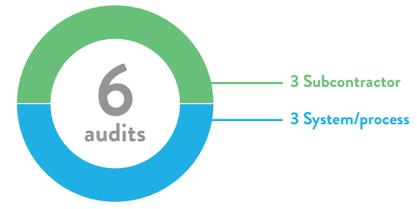
Studies per research area



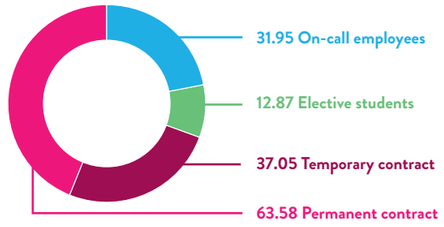
Number of external audits



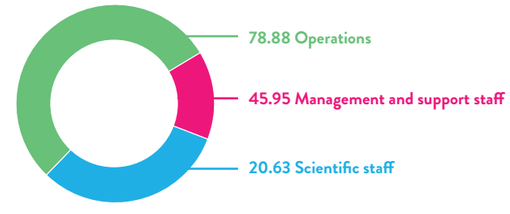
Number of internal audits



FTE by contract type



FTE by department



Growing towards the future

Looking back on the past few years at CHDR, the most striking development has been our growth in terms of the number, duration, and intensity of studies. And a little less obvious – but just as important – are the preparations for future developments. CHDR is exploring new ways to study pharmacological effects in early clinical drug development and new approaches to clinical research.

CHDR is a not-for-profit foundation, which places the company in a unique position among contract research organisations (CROs). All of CHDR's revenues from contract research are used for further development, scientific research, and education. This gives CHDR a competitive advantage in the rapidly changing world of drug development. As reflected in this annual report, CHDR has grown in terms of turnover; in addition, CHDR has invested heavily in developing new approaches to investigate the pharmacological effects of compounds in a wide range of research areas. For example, CHDR researchers have developed new biomarkers. Imaging techniques such as PET and resting-state fMRI play an increasing role in research, and dedicated techniques have been developed in the fields of dermatology, CNS research, and immunology. In each of these areas, CHDR makes creative use of existing techniques, thereby converting these techniques into tools for clinical pharmacological purposes. For example, although driving simulators and PET scanners were not initially developed to study drug effects, these tools can be extremely useful when adapted to answer the right questions regarding new medicines.

New developments

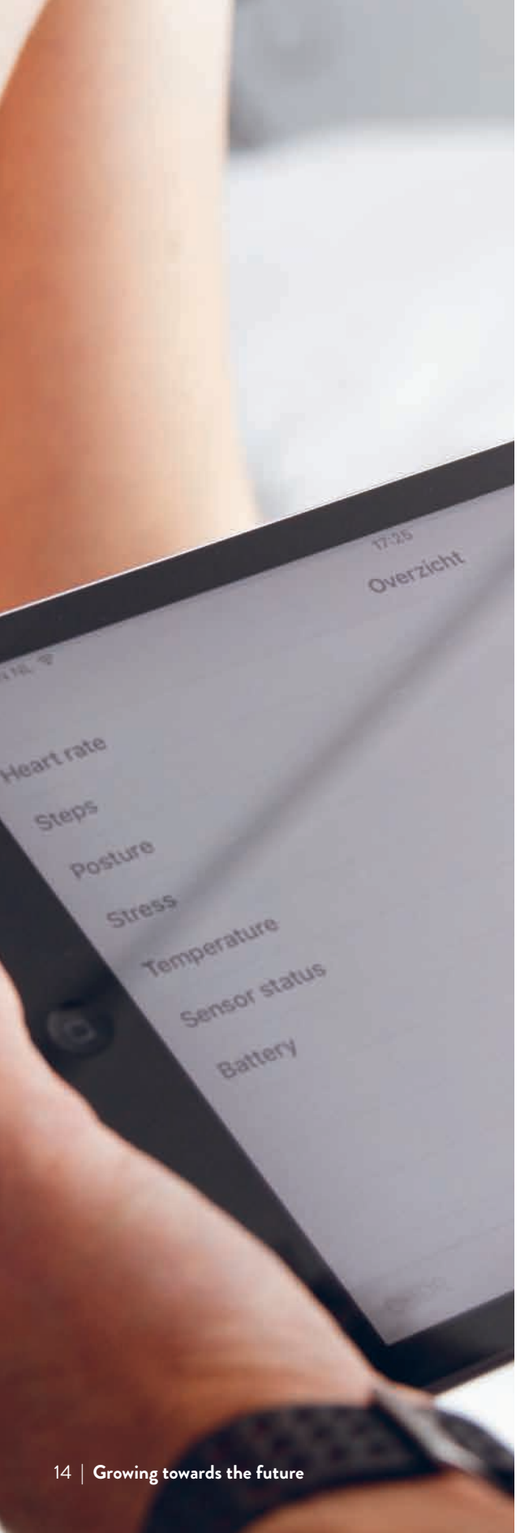
Several new approaches are changing our view of drug development, which has traditionally been seen as a step-by-step process. Increasingly, development of a new product starts in a small company, usually a spin-off from academic research. Thus, many new products are aimed at extremely specific groups of patients. As a result, precision medicine is rapidly becoming a reality. But precision medicine involves more than just drugs; it also involves combinations of pharmacological interventions, devices, software, nutritional interventions, and lifestyle recommendations, all of which can be monitored using an e-health app.

Some of these developments have already had an impact on drug development, and others are soon to follow. Thus, the traditional role of the CRO is about to change at a fundamental level. The details of this change are not yet known, but it seems logical that the development of new medical interventions will become more multidisciplinary and will involve multiple companies and/or facilities. In this respect, the Netherlands is well-positioned to play a key role in this process.

'As a not-for-profit foundation, CHDR enjoys a unique position among CROs. Because all of CHDR's revenues are used for development, research, and education CHDR has a competitive advantage in the rapidly evolving world of drug development.'

The Netherlands offers high-quality research in medicine, life sciences, and technology; moreover, the geographical distances between institutions are relatively small, and the Dutch culture facilitates collaboration rather than competition. Indeed, the Netherlands can be considered one large research institution, with CHDR as its drug development office.

Another important common denominator in the development of new drugs and medical approaches is the high cost; therefore, it makes sense to obtain as much relevant information as possible – and as early as possible – in order to make sound investment decisions. CHDR's approach has always been to maximise the



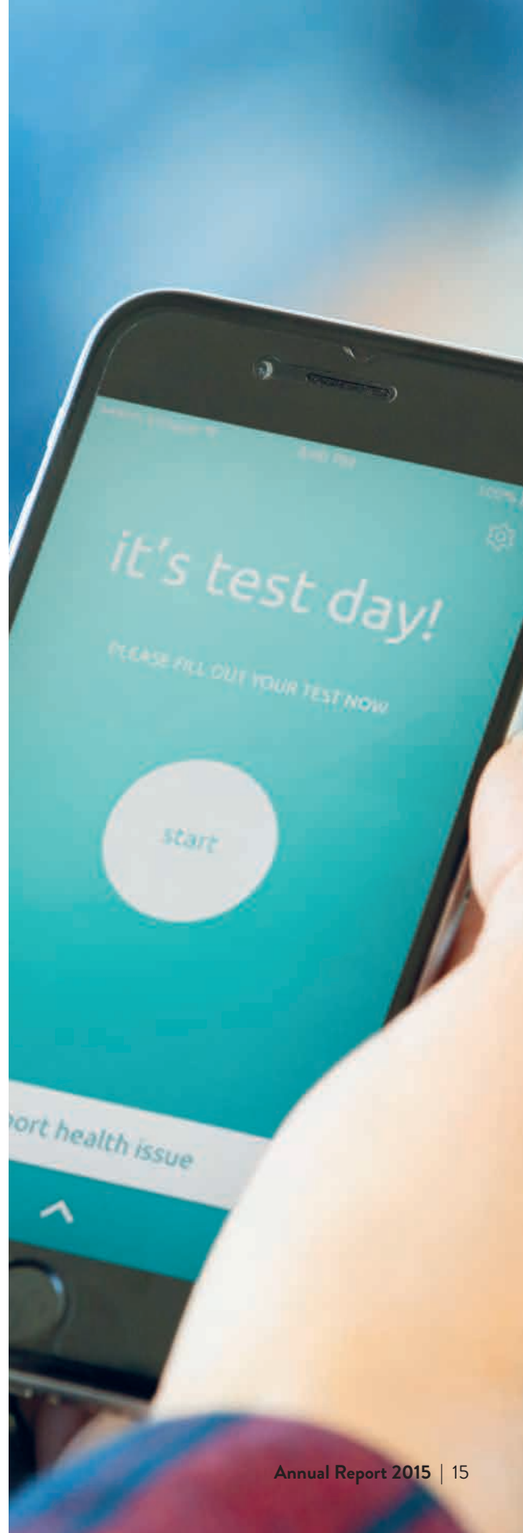
amount of knowledge collected in the earliest stages of drug development. That's why CHDR has invested in test batteries (for example, NeuroCart and PainCart), biomarker research, imaging, and other cutting-edge methods to analyse pharmacological effects. In this way, CHDR researchers help sponsors make rational decisions in the development of new treatments.

At the same time, developing more 'personalised' treatments increases the challenges associated with recruiting subjects when the compound is ready to be tested in patients. Patients who meet the inclusion criteria will be treated in many different research centres; however, the use of sophisticated biomarkers and other tools is nearly impossible in a multicentre setting. CHDR's solution is the Monocentre Strategy, in which patients who wish to participate in a study will be driven to a comfortable, well-equipped central facility. In addition, CHDR is currently screening cohorts of patients with the same diagnosis in order to facilitate protocol development and recruitment using their unique 'Ready-for-Research' approach.

Growth models

In 2013, CHDR moved to a new building in order to accommodate the growing number of requests for drug trials. In 2015, even this new building was booked to capacity on several occasions. With careful planning and scheduling, there is of course still room for growth; however, CHDR is also developing other strategies to accommodate growth without the need to move into another building. One such strategy is CHDR's Trial@Home, which was used successfully in several dermatology studies in 2015 (see page 23). The basic idea is simple: once the compound is found to be safe, much of the subsequent clinical research can be done by 'remote', with the subjects staying comfortably at home. Using portable monitoring devices and e-health applications, CHDR can monitor the subjects' health and collect data remotely. This novel approach allows for longer follow-up period, produces more realistic data, and significantly lowers costs.

In some cases, a study can be performed by CHDR staff at other locations. For example, CHDR has a clinical research unit at the VUmc in Amsterdam. At the Radiology Department at Leiden University Medical Centre, CHDR has full access to a dedicated MRI scanner for performing resting-state MRI studies of the brain; this facility also houses space for running additional tests, including NeuroCart, PainCart, and other procedures. In short, CHDR is developing strategies that enable its researchers to meet future demands.



Highlights

Closing the investment gap in product development

The challenge

Taking the next step with promising new therapies

Imagine you're a scientist who's created a promising new therapy for Alzheimer's disease. You want to bring this therapy to the market, so you started a company to develop it. Soon, you will likely face a classic dilemma in drug development: to attract funding, you need to show investors positive initial results; but without funding, you cannot conduct the necessary preliminary research. Because of this dilemma, many start-up companies – and their brilliant ideas – have perished in this 'investment gap'. Even if you do find investors, they'll probably demand a share in your new company, reducing your decision-making freedom and diluting your equity.

'At CHDR, we often encounter young companies that have excellent ideas but are backed by unnecessarily complex financing schemes for sub-optimal clinical trials. Our approach will give these companies more bang for their buck.'

The solution

Venture loans to help researches reach micro-milestones: the 123 Innovation Initiative

To give starting biotech companies a helping hand, CHDR developed the 123 Innovation Initiative. The aim of this initiative is to provide non-dilutive financing for early-stage clinical trials that are more effective, informative, and efficient. At 123, three partners work together: a starting pharmaceutical or biotech company, a group of investors, and CHDR. Using CHDR's 'question-based drug development' approach, the most important questions (i.e. the micro-milestones) are identified, and a trial is conducted to answer these questions. Because the Initiative provides a venture loan to the company, research can be financed without diluting equity. If the trial results are encouraging, the value of the compound increases, and attracting additional funding is easier.

As an example, when developing a new drug for Alzheimer's disease, it's essential to show that the compound reaches its target within the subject's brain. This is exactly the type of question that CHDR can help answer. If the compound indeed reaches the brain, investigators can take the next step. If not, it is good to know this as early as possible; this way, the company can go back to the drawing board without wasting money on further clinical research.

The result

A win-win-win solution

123 is a relatively new initiative. Despite its youth, however, the first 'proof-of-principle' test has shown that the concept is sound, and it has attracted the interest of both companies and investors. Companies see the potential to bridge the investment gap, and investors see a wise short-term investment with relatively high returns and limited risk, thanks in part to CHDR's expertise. The Initiative is – of course – also an attractive way to reach promising new investment opportunities. For CHDR, the Initiative is yet another way to do what CHDR's researchers do best: solve complex puzzles while contributing to high-quality drug development.

Conclusions

Combining investors, CHDR's expertise, and new companies with promising new medicines significantly increases the likelihood of success by bridging the investment gap and helping reach market authorisation faster.

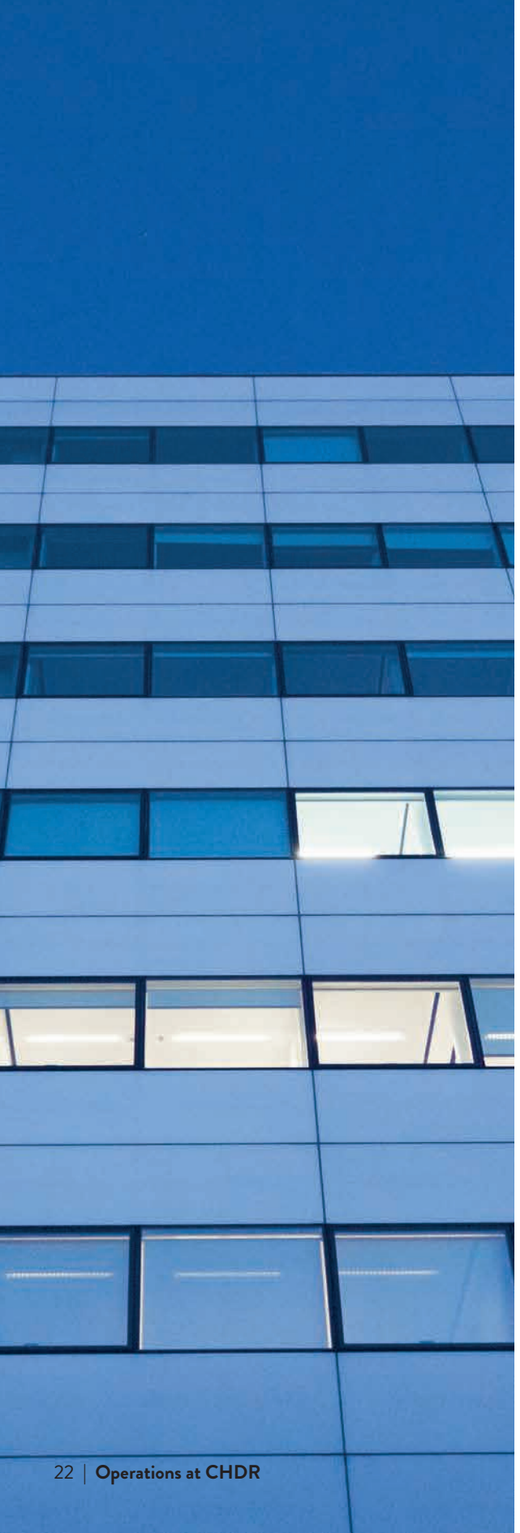
‘Perfectly suited to providing innovative research’

Every aspect of a study at CHDR is well-thought-out and clearly executed. This approach is evident even from minor operational aspects such as their IT infrastructure and the design of their building and office space to optimise patient management and patient flow. Our work with CHDR is generally geared towards developing new methodologies; so by definition it’s highly innovative. CHDR is uniquely suited to tackle difficult scientific problems and challenges. Importantly, CHDR’s researchers are driven by an innate curiosity.

Experimental Medicine Director
Large Biotech Firm*

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

Operations at CHDR



Adapting to growth

In the past few years, CHDR has grown considerably. Facilitated in part by our new, larger building, the number of studies at CHDR has increased steadily. At the same time, the studies themselves have become more complex due to several factors, including a larger number of studies in patients. In 2015, organisational changes were needed in order to accommodate this growth.

To execute a study plan, many elements within CHDR and its partners must work together smoothly. Many seemingly unrelated factors must be taken into account, including ethics committee approval, subject recruitment, logistics at the LUMC Pharmacy, staff planning, managing blood samples and data, and catering to the needs of the subjects who stay at the facility. Planning ahead is paramount, but plans often change due to unforeseen circumstances. One can imagine that this becomes exponentially more complex when the entire organisation is growing, the number of studies and subjects increases, and the studies themselves become more complicated.

More people

Through 2014, much of the growth at CHDR was accommodated by increasing staff workload and by hiring temporary employees. At the end of 2014, CHDR realised that it needed to increase the size of its nursing staff. So during the course of 2015, an additional 25 personnel were hired, with the majority joining the nursing staff. At the operational level, a dedicated Manager was appointed to the Clinical Unit. In addition, a new project was launched to adapt the entire organisation to the larger scale of operations. At the end of 2015, a round-the-clock nursing schedule was introduced. Lastly, new study planning software was installed and will become fully operational in early 2016.

Future developments

When the new building opened in 2013, the number of beds increased from 24 to 60. At the time, it didn't seem likely that full capacity would be reached anytime soon; in fact, the building was estimated to be large enough to accommodate growth through the next 15 years. But in the summer of 2015, the facility's 60-bed capacity was exceeded on more than one occasion. This was not really a surprise: by 2015, the number of studies at CHDR had increased considerably. And the forecast for 2016 is just as promising, so last year's record may soon be broken. If this trend continues,

'CHDR plans to grow in a variety of ways. One key approach is to increase the number of subjects who are monitored from home using Trial@Home.'

CHDR will soon outgrow even the new building. With such rapid growth, we need to work hard to keep CHDR's culture intact. Values such as transparency, open communication, and dedication to both science and service made CHDR what it is today, and these values will continue to shape CHDR's future.

On the other hand, increasing the number of subjects who stay at the facility is not CHDR's only strategy. Instead, CHDR plans to grow in a variety of ways. One key approach is to increase the number of subjects who are monitored from home using Trial@Home. Because the nature of clinical studies is changing, data-intensive studies in patients and/or elderly populations requires subjects to spend several weeks at CHDR. Meeting these challenges will require adapting CHDR's operations infrastructure, and there is no doubt that our staff will rise to the challenge.

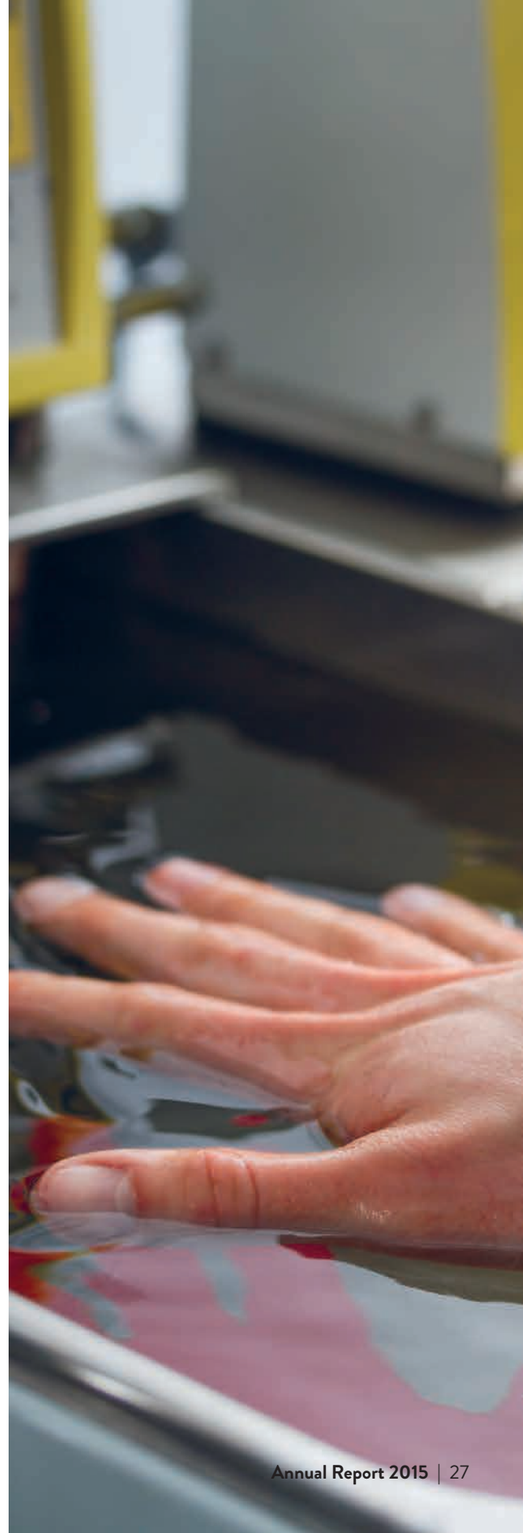
Pain and neuro-degeneration

In the realm of CNS research, CHDR is particularly interested in therapies for treating pain and neurodegeneration. Using two comprehensive test batteries – PainCart® and NeuroCart® – the pharmacological effects of candidate drugs can be measured early in clinical development.

In the past year, several important studies were performed in the therapeutic areas of pain and neurodegeneration. Three of these studies were designed to test first-in-class analgesic compounds. In two studies, researchers used PainCart to demonstrate a clear analgesic effect. By comparing the effects of these test compounds on different types of pain with earlier established profiles of current analgesic drugs, researchers were able to make recommendations regarding further clinical research. One compound, a blocker of tropomyosin receptor kinase (Trk) receptors, produced a profile that was similar to ibuprofen. The profile of another compound, an agonist selective for GABAA receptors containing α2/3 subunits, was comparable to the profile of pregabalin, a drug commonly used to treat neuropathic pain. The third compound, which had no measurable effect on pain scores, was discontinued in phase 2 due to its lack of efficacy, preventing the need for further testing.

'By comparing the effects of these test compounds on different types of pain with earlier established profiles of current analgesic drugs, researchers were able to make recommendations regarding further clinical research.'

Researchers have also continued testing candidate drugs for treating Alzheimer's disease, for example in healthy elderly subjects. These tests use CHDR's NeuroCart, a comprehensive battery of tests for measuring neurophysiology and cognition. To illustrate this approach, CHDR studied a selective M1 muscarinic acetylcholine receptor agonist that belongs to a class of drugs that has shown promising effects in preclinical models of Alzheimer's disease. Unfortunately, muscarinic receptor agonists often have adverse side effects by acting on muscarinic receptors in the autonomous nervous system. These side effects can include hypersalivation and hypertension. Therefore, the agonist being studied at CHDR was designed to improve cognitive function without these unwanted side effects.



Highlights

Using the statin challenge to measure mitochondrial function

The challenge

How can we measure the effects of compounds that improve mitochondrial function in healthy subjects?

New drugs are currently being developed to slow neurodegeneration by improving mitochondrial function. Before these drugs can be tested in patients, however, researchers at CHDR must determine whether these drugs are both safe and effective in healthy subjects. This creates a pharmacological catch-22: how can you measure a compound's effect on mitochondrial function in subjects whose mitochondria already function optimally?

The solution

The statin challenge – pharmacologically reduce mitochondrial function in healthy subjects

At CHDR, researchers use the 'pharmacological challenge', a clever trick to slow or 'tone down' a biological process in healthy subjects; the effects of the candidate drug can then be tested. For example, cognitive performance can be impaired slightly by giving healthy subjects the muscarinic acetylcholine receptor antagonist scopolamine. If the candidate drug restores cognitive function in this context, this can provide evidence that the drug acts upon the appropriate pharmacological target.

With respect to improving mitochondrial dysfunction, the statin challenge is based on a common side effect associated with the cholesterol-lowering drug simvastatin. After four weeks on a normal therapeutic dose of simvastatin, subjects develop mild – but measurable – mitochondrial dysfunction (reduced production of mitochondrial coenzyme Q10), providing researchers with a model in which to study the effect of candidate drugs designed to improve mitochondrial function.

'We are now ready to use the statin challenge to evaluate compounds designed to improve mitochondrial function in neurodegeneration. The next step is to test an experimental compound both in healthy subjects and in patients with Huntington's disease.'

An easy method for studying mitochondrial function is to measure energy metabolism in the subject's muscle tissues. Using ^{31}P-MRI spectroscopy, we can measure the concentration of phosphocreatine, an important secondary energy source in muscle cells. During exertion, phosphocreatine is dephosphorylated and must be re-phosphorylated using ATP produced by the mitochondria. Thus, measuring phosphocreatine recovery time provides a useful, non-invasive measure of mitochondrial function. In the experimental setup, the subject is instructed to exercise a muscle while in an MRI scanner, and phosphocreatine recovery time is measured.

In the statin challenge, a healthy subject takes simvastatin for four weeks to mildly reduce mitochondrial function. After four weeks, the test compound is given, and its effect on mitochondrial function is measured and compared to the patient's baseline and 'toned down' levels. As a proof-of-principle, CHDR used the statin challenge to show that coenzyme Q10 can restore mitochondrial function in healthy subjects.

Results

A validated model

In a pilot study at CHDR, the statin challenge performed exactly as predicted. First, subjects who received a four-week course of simvastatin had measurably increased phosphocreatine recovery time, reflecting impaired mitochondrial function, and 30 days of coenzyme Q10 increased mitochondrial function.

This pilot study included other important measures of mitochondrial function in addition to ^{31}P-MRI spectroscopy. Near-infrared spectroscopy (NIRS) did not reveal a change in mitochondrial function; however, testing mitochondrial permeability in blood samples showed results consistent with MRI spectroscopy. Another test performed in collaboration with Erasmus Medical Centre in Rotterdam showed that simvastatin increases oxygen consumption, consistent with mitochondrial uncoupling.

Conclusions

Simvastatin is a safe tool for reversibly lowering mitochondrial function in healthy subjects, enabling researchers at CHDR to test candidate compounds designed to improve mitochondrial function in patients with neurodegenerative disorders.

NeuroCart

The CNS research unit has always been one of CHDR's strong suits. Now that the number of studies in both healthy subjects and patients has increased, 'upscaling' is the operative word. However, increasing our focus on studies in patients also requires restructuring the operating procedures. Consistent with these changes, NeuroCart is now being used to study the effects of disease and other clinical features, including fatigue.

Over the past 25 years, NeuroCart has evolved into an extremely useful tool in early-phase studies of CNS drugs. The individual NeuroCart tests have been validated, the procedures are well-described, and sponsors now know what to expect from this comprehensive neurological test battery. With that said, times are changing, and NeuroCart will change as well; for example, the user interface will be more user-friendly, making it easier to use with less extensive training

User-friendly

A few years ago, CHDR had four NeuroCart setups operated by a limited number of research assistants. Today, CHDR has more than ten fully operational NeuroCart setups. This growth has been accommodated by hiring more trained research assistants. Moreover, CHDR increasingly uses NeuroCart in external settings, where less supervision is available, including the PET facility at VUmc in Amsterdam and the pharmacological MRI facility at LUMC in Leiden. In the future, individual NeuroCart components might even be used by the subjects themselves in a Trial@Home setting (see page 44).

In 2015, the first steps were made towards developing a more user-friendly interface, for example by automating certain steps. Of course, these changes need to be validated. Moreover, before the next-generation NeuroCart is ready to leave CHDR, it will undergo rigorous testing to ensure its validity and reliability in other situations.

NeuroCart and the Ready-for-Research approach

A novel NeuroCart application is currently being developed in collaboration with a sponsor from outside the field of pharmacology: an organisation of surgeons is interested in developing a system to objectively measure how working the night shift can affect a surgeon's performance. In this respect, NeuroCart is ideal, as it includes tests to measure general alertness, hand-eye coordination, alertness levels while performing a routine task, and much more. At CHDR, this research is particularly relevant, as it correlates pharmacology with clinical symptoms. It may also provide CHDR with a new benchmark for quantifying side effects, for example by comparing the effect of a drug with losing a night's sleep. Along the same lines, NeuroCart results can be compared with driving performance measured using Green Dino's driving simulators, which CHDR recently obtained for use in drug studies. Together, all of these applications will help clinically validate NeuroCart, which is particularly important for patient studies.

NeuroCart will also be used in patients with neurological and/or psychiatric disorders before the subjects receive any pharmacological compounds. Thus, NeuroCart's comprehensive neurological test battery will enable researchers to quantify symptoms and track the course of the disease, as these same patients may later participate in a pharmacological study. This novel CHDR concept of recruiting patients before a study protocol even exists is called 'Ready-for-Research'.

Amphetamine challenge

Another concept that has been instrumental in studying early-phase pharmacological effects at CHDR is the pharmacological challenge (see also page 28). Demonstrating a beneficial effect of a compound within a specific neurophysiological system can be difficult in healthy subjects, as these systems may already function at optimal levels. For example, a drug that is designed to reduce hallucinations in psychotic patients may not have a measurable effect in healthy subjects who do not experience hallucinations. In a pharmacological challenge, a specific function is reduced temporarily in healthy subjects, enabling researchers to test the effect of the study compound.

In 2015, CHDR researchers showed that dexamphetamine, a drug used to treat attention deficit disorders, not only has measurable effects on the dopaminergic system (which is involved in psychosis), but also causes sensitisation of some brain functions. This finding makes dexamphetamine an interesting tool for studying new compounds being developed to correct maladaptive processes in the CNS, including psychiatric disorders such as addiction and psychosis.

‘This novel CHDR concept of recruiting patients before a study protocol even exists is called “Ready-for-Research”.’

Highlights

Measuring the profile of a new sleep aid

The challenge

How can we establish the dose, efficacy, and side effects of a new sleeping pill?

Orexin antagonists are a relatively new class of medications for patients with sleeping disorders. The mechanism of action is based on orexin, a hypothalamic neurotransmitter involved in wakefulness. For a clinical pharmacologist, the challenge is establishing which dose helps the patient fall asleep without interfering with daily life (for example, does not cause drowsiness or other side effects the next day). Ideally, the patient should still be able to perform routine tasks after taking the medication, for example driving a car. Importantly, given that many types of sleep-aid medications are currently available, it would be good to show the added benefits of orexin antagonists compared to other classes of drugs. In the study, the sponsor wanted to learn as much as possible from early clinical trials by including healthy subjects as well as patients with insomnia.

The solution

A comprehensive test battery, including a virtual driving test

CHDR has extensive experience with other orexin antagonists, including the first such drug in this class, which led to a publication in *Nature Medicine* in 2007. NeuroCart reliably predicted the effects of the drug and was used to establish the optimal dose. Thus, the new compound's profile can be compared to historical data, as well as to the commonly used GABAergic sleep aid zolpidem. Using NeuroCart, CHDR performed the first-in-human studies with the new orexin antagonist.

'By building on our earlier work, we successfully determined the optimal dose for treating insomnia. We are now preparing for future studies in which we'll investigate the beneficial effects of this compound in other conditions such as depression.'

To test whether the new sleep aid affects driving skills, CHDR used a novel approach: a driving simulator. The driving simulator can be used to perform a test comparable to the current gold standard: driving as straight as possible on a real road. In this respect, the simulator is both safer and easier than performing the test on an actual road, and it offers the possibility of incorporating additional tests (i.e. standardised interruptions). According to a recent FDA publication, a driving simulator can provide informative and reliable information regarding a drug's actual effects on driving performance.

All of the patients included in the phase 2 multicentre study had insomnia, which was confirmed using polysomnography at CHDR's sleep laboratory. This is an important step, as subjective reports of insomnia do not necessarily reflect actual sleep duration and/or quality.

Results

In the first-in-human studies conducted at CHDR, the new compound's NeuroCart profile was similar to the first orexin antagonist's profile, and multiple ascending dose studies yielded the optimal dose. At this dose, subjects performed significantly better on the NeuroCart after taking the study compound compared to a dose of zolpidem that had similar sleep-inducing effects. Based on these initial findings, the sponsor can now determine the dosages to be used in clinical studies with patients.

Conclusions

The NeuroCart test battery can be used to determine the optimal effective dose for new CNS drugs. NeuroCart is also valuable for comparing new compounds with well-known drugs with respect to both desired effects and undesired side effects.

‘CHDR gives clear added value’

Because CHDR is a non-profit organisation, they stand out from other CROs. CHDR channels their revenue back into training, and they are closely involved with the medical school. I’m not aware of any other CRO that does this. Other CROs deliver only standard endpoints, whereas CHDR gives clear added value.

I see CHDR as lying somewhere between a supplier and a business partner. Thus, CHDR is clearly a supplier in the sense that we pay them to conduct our clinical studies, but they also add considerable value as a conventional CRO, based on their in-depth academic background, expertise, and knowledge. In particular, their academic expertise is extremely valuable.

Senior Clinical Director
Top 10 Big Pharma Company*

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

Innovation through multi-disciplinary collaborations

Within the fields of cardiology, vascular medicine, surgery, immunology, and internal medicine, CHDR introduced several new services and conducted several sponsored studies. For example, a novel compound was studied both in healthy subjects and in patients with psoriasis. Also, several new methods have been developed for use in future studies.

Cardiology

CHDR's Cardiology Services are now fully operational. These services are designed to answer relevant questions regarding the effects of new drugs on the cardiovascular system, including comprehensive QT studies. By combining these services with the clinical studies already being performed at CHDR, early drug development becomes essentially a one-stop shopping experience. This is important to sponsors, as other parties are not needed and all study-related data are stored in one convenient database. Several sponsors have already used these new services. In addition, CHDR has the unique opportunity to perform more comprehensive research on the cardiovascular system. In the context of Cardiology Services, CHDR has strengthened their collaborations with cardiologists at several university medical centres and other hospitals. As an added benefit, recruiting patients for clinical studies is also easier.

Wearable sensors

An exciting new development in the fields of cardiology and internal medicine will be the use of wearable adhesive sensors to monitor heart rate, body movement, respiratory rate, temperature, and other variables outside of the study centre. The sensor transmits data via Bluetooth to the patient's cell phone (or to a PDA provided by CHDR). The advantage of this approach is that it provides continuous monitoring for days, weeks, or even longer. The wearable sensors are easier to use than the classic Holter monitors, and they record more variables. For example, the motion sensor will register if the subject falls due to cardiac arrhythmia or other side effects such as drowsiness. As part of CHDR's Trial@Home, these wearable sensors are likely to become an invaluable tool in drug development.

Microvasculature

Although cardiac activity and blood flow through major blood vessels can be measured relatively easily, smaller blood vessels such as arterioles, venules, and capillaries are more difficult to study. However, because these tiny vessels play important roles in several physiological processes, it is important to study them in the context of drug development. In 2015, two approaches – dynamic light scattering in the skin and advanced retinography – were used to study microvasculature. Advanced retinography was relatively easy to validate and will be used in studies planned for 2016. The interior of the eye offers a unique view of the smallest blood vessels, enabling researchers to study blood flow dynamics. For example, researchers are using these methods to quantify the interaction between blood and the endothelium. And of course, changes in ocular microvasculature play a role in various diseases of the eye itself, and many systemic diseases (e.g. diabetes) have ophthalmological complications. The use of retinal blood flow measurements has led to an important collaboration between CHDR and the Rotterdam Eye Hospital, and collaborations have also been established with groups that study thrombosis and with haematologists who study changes in blood flow in conditions such as sickle-cell anaemia.

Highlights

Dermatology studies are more effective with Trial@home

The challenge

How do we conduct a large phase 2 dermatology trial with maximum adherence and objective results?

To reliably measure the effect of a new dermatological treatment, the treatment must be applied at regular intervals for several days. Ideally, the subjects' adherence to the protocol is optimised and measured. And of course, the results have to be verified objectively.

The solution

Trial@home

CHDR researchers have used Trial@home to conduct studies in dermatology and gynaecology. One study examined the effects of applying a new medication daily for 42 days in 80 patients with human papilloma virus–related conditions. Another study examined a treatment for eczema in 36 patients. A third study – which began in 2015 and is expected to run until the start of 2017 – is examining the effects of a new treatment for vulvar intraepithelial neoplasia, a precancerous lesion of the vulva that is caused by a strain of human papilloma virus.

For these trials, patients were recruited primarily via advertisements placed in media outlets and through the Dutch Dermatology Trial Network, which includes more than 180 dermatologists in the Netherlands. Some patients were recruited through other medical specialists or through their general practitioner. Each candidate participant visited CHDR for examination. If the patient met all of the inclusion criteria and provided informed consent, he/she received the study medication with instructions for use, plus something special: either an app for his or her iPhone or (if the participant did not have an iPhone) an iPod pre-loaded with the app. The app, which was designed specifically for the study, served several key purposes: the app reminded the patient to apply the medication at designated times, and the patient then used the app to take a picture of the application area, which confirms that the medication was applied (in the study involving vulvar intraepithelial neoplasia, the patient was asked to document the open medication tube). Importantly, the patient also used the app to answer daily questions regarding complaints such as pain, itching, or irritation, as well as questions regarding quality of life. Using the app, all study data are encrypted and securely transferred to the CHDR server at regular intervals.

During the study, patients were asked to return to the CHDR facility on several occasions to assess the effect of treatment using more advanced techniques. For example, in the eczema study, a high-resolution 3D camera was used to measure lesion size and to quantify the degree of 'roughness'. CHDR has also developed a 'DermaToolbox', a collection of robust tools for objectively characterising skin lesions, including high-resolution 2D and 3D photography coupled with laser Doppler imaging, transepidermal water loss measurements, and lesion biopsies for biochemical profiling.

Results

High patient compliance and high-quality data

For the three studies described above, three specific mobile apps were developed and fully validated.

Importantly, the results confirmed that Trial@home is highly feasible, with extremely high patient compliance (>90%). Because the app is completely mobile, data can be collected off-site, and a large number of data points can be obtained with little effort. Compared to the traditional approach using a written diary, the app increases both patient compliance and the quality of the data. With the app, the researcher knows precisely when the data was collected. Another valuable feature of the app is the ability to proactively monitor patient activity, which is particularly important during the first few days and weeks of a study. For example, if a patient has not transferred the data for several days, the researcher can contact him/her and solve any problems early.

Conclusions

Mobile technology (i.e. apps installed on mobile devices such as iPhones and iPods) greatly increases both patient compliance and data quality. Together with the high-tech measurements performed on-site at CHDR, these apps form the basis of the Trial@Home system. Patients like that they can participate in a study with minimal interference in their daily lives, and researchers like that they can receive daily data points from a large number of participants.

'Trial@Home is ideal for conducting long-term dermatology studies. We've also learned quite a lot regarding developing mobile apps and several practical aspects, and we will expand the concept to other research fields in the near future.'

Image-guided surgery

Collaborations lead to revolutionary surgery

Fluorescent probes are a powerful new weapon in the battle against cancer. At Leiden University Medical Centre, surgeons worked closely with pharmacologists at CHDR and mathematicians at Leiden University to develop this technique.

Two years ago, Mr Gijs de Vries*, a 66-year-old retired geography teacher, was diagnosed with colon cancer. Mr de Vries was treated surgically, and the pathologist confirmed mucinous adenocarcinoma in the sigmoid colon. At his most recent follow-up visits to the outpatient clinic, tests revealed that blood levels of the tumour marker were rising, and an abdominal PET-CT scan was ordered.

Dr Charlotte Hoogstins, investigator
'There's so much to learn – the pharmacology, the technical aspects, the organisation, and the ethics of first-in-human research. Going back and forth between LUMC and CHDR gives us the best of both worlds.'

Monday, November 16, LUMC:
The surgeon informs Mr de Vries that these test results suggest possible localised recurrence of the tumour. The surgeon recommends exploratory surgery and possible removal of the recurrent tumour. He also tells Mr de Vries about an exciting new clinical trial using fluorescent probes to visualise the tumour cells. Mr de Vries asks for further information.

Dr Charlotte Hoogstins, one of the trial's investigators, meets with Mr and Mrs de Vries and explains that prior to the surgery, Mr de Vries will receive an infusion of an experimental compound containing a fluorescent antibody that recognises a specific target present only on colorectal cancer cells, allowing the surgeon to 'see' the cancer cells using a specialised camera during the surgery.

Friday, December 12, LUMC:
At the LUMC pharmacy, Linda van der Hulst, the pharmacist and trial coordinator, prepares 150 ml of the fluorescent marker.

Saturday, December 13, CHDR:
Dr Hoogstins and her colleague Dr Noor Boogerd welcome Mr and Mrs de Vries to the CHDR facility. Mr de Vries is prepped for the infusion.

Prof dr Koos Burggraaf, CHDR
'We are constantly improving the procedure. For example, Prof Bert Peletier and his team are currently developing a kinetics-based model to predict the optimal dose and time window for administering the compound. It's fascinating to be able to literally see what a compound does.'

After the infusion, Mr and Mrs de Vries spend a relaxed day at the facility. At regular intervals, a nurse monitors Mr de Vries, checking his blood pressure and pulse and taking occasional blood samples, which will be sent to a specialised laboratory for analysis and kinetics modelling.

Prof dr Bert Peletier, Leiden University Mathematics Institute
'What I like about this collaboration is that I am part of the team, not a number cruncher. We discuss the kinetics of these compounds and try to model their behaviour.'

Monday, December 14, LUMC:
Mr de Vries arrives at the surgical ward and receives his pre-op medication.

Dr Alex Vahrmeijer, surgeon and project leader, LUMC
'This kind of research requires a dedicated team. Everyone involved, including the pharmacist, pathologist, anaesthesiologist, and clinical pharmacologist should be on the same page. In this respect, we're fortunate to have so many enthusiastic people on board.'

During surgery, Dr Vahrmeijer examines the previous surgical site and finds an enlarged lymph node, which he plans to resect.

To help Dr Vahrmeijer see where to cut, Dr Hoogstins positions the sterile imaging system over the surgical site while her colleague, Dr Boogerd, operates the viewing screen. In real time, both fluorescence images and standard images are shown on the screen. The enlarged lymph node is brightly fluorescent, showing the precise location of the malignant tumour cells. Dr Vahrmeijer can now confidently remove the affected lymph node.

Dr Boogerd and Dr Hoogstins take the resected lymph node to the Pathology Department, where they examine the tissue using a fluorescence imaging system. Based on this examination, frozen sections are prepared for detailed study using fluorescence microscopy, which confirms the presence of cancer cells in the lymph node.

Following the surgery, Mr de Vries recovers fully and is discharged.

Maaike Vinkenburg-van Slooten, project coordinator
'These multidisciplinary collaborations are the future of innovative research. Combining the kinetics and effects of a compound at an early stage, and using the best available models – it all comes together here.'

**This story is based on actual events; only the patient name is fictional.*

Highlights

Lighting up tumour cells with fluorescent probes to show the surgeon where to cut

The challenge

What are the best conditions (timing, dosage, etc.) for administering a fluorescent marker to detect a tumour?

In collaboration with several surgical departments at LUMC, CHDR researchers have been developing applications for using fluorescent markers in surgery. Discriminating between healthy tissue and tumour tissue during surgery can be quite difficult, particularly with minimally invasive surgery. To overcome this challenge, fluorescent labels can be conjugated to monoclonal antibodies that recognise the tumour cells. Thus, the tumour tissue is selectively labelled, enabling the surgeon to efficiently remove malignant tissue while maximally sparing healthy tissue. This approach can also be used to identify malignant tumours during a colonoscopy exam and other endoscopic procedures.

Of course, these fluorescent markers work best only when the dose and timing of administration are ideal. For example, if the marker is administered too close to the time of surgery, the marker may not reach the tumour in time, or the background signal might be too strong in the healthy tissues. On the other hand, if the marker is administered too early, the fluorescent antibodies might be washed out prior to surgery. And – of course – the dosage must be optimised in order to achieve the best contrast between the tumour cells and healthy tissue.

‘This project is the culmination of successful multidisciplinary collaborations. Bringing together surgeons, biologists, and mathematicians – and of course our sponsors – has helped.’

The solution

Develop mathematical models for optimising conditions

The uptake, target binding, and elimination of these fluorescent antibodies can be modelled using an approach similar to modelling pharmacokinetics and pharmacodynamics. However, this is no easy task. Many factors can affect the antibody’s journey through the bloodstream, target binding, and elimination. Some of these factors are specific to the procedure and/or the type of compound, whereas other factors are specific to the patient and/or tumour. Because the success of surgery depends –at least in part – on the degree of contrast between non-fluorescent healthy tissue and fluorescent tumour tissue, optimising both the timing and dosage are essential to achieving the best possible outcome.

CHDR is fortunate to collaborate with top-level mathematicians such as Prof. Dr Bert Peletier to develop several robust techniques for modelling these parameters.

Results

A practical set of parameters to optimise dosage and timing

Thanks to the efforts of basic scientists, surgeons, pharmacologists, and mathematicians, a working model has now been developed. From this process, it has become increasingly clear which general and specific parameters must be measured in order to optimise thet dosage and timing of fluorescent markers.

One of the advantages of this research is that the models’ predictions can be verified quite easily. For example, the absence or presence of fluorescence in relevant tissues can be measured, and the surgical outcome can be confirmed histologically. Based on these promising results, fluorescent markers are ideal molecules for further developing kinetics-based models for other high molecular weight compounds. For example, CHDR will use similar fluorescence-based technologies to study peptide vaccines. Moreover, the knowledge obtained from these experiments and modelling approaches will also be applied to the study of biologicals and biosimilars.

Conclusions

Combining powerful mathematical models with clinical research has helped surgeons optimise the dosage and timing of fluorescent labels for use in minimally invasive tumour-removal surgery.

Working with CHDR

‘More than just a supplier’

Although I would describe CHDR as a supplier, the way they interacted with us was more in line with a valued partner. CHDR went out of their way to assist us and provide support, which was greatly appreciated. For example, we asked CHDR to perform additional work after the study was completed, and they did so without hesitation. When it became difficult to obtain suitable volunteers, CHDR put all of their efforts into recruiting subjects. And when the study was in danger of falling behind schedule due to unforeseen circumstances, CHDR arranged extra volunteers in order to get back on schedule.

Director, Clinical Operations
Large Biotech*

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

Translational biomarkers

When testing a compound in humans, many questions must be addressed. For example, does it live up to its promises (for example, does it really reduce inflammation)? And what are its unintended effects, if any? To help answer these questions, CHDR's Translational Biomarkers group selects and develops novel 'wet' biomarkers and innovative bioassays to support the transition from preclinical studies to clinical research. In 2015, work in this area primarily involved various aspects of immunology and cellular stress by detecting both intended and unintended actions of novel compounds, thereby laying the groundwork for future studies.

A biological 'seismograph' of drug effects

Biomarkers play a crucial role in demonstrating pharmacological effects in early clinical drug development, and they help sponsors make rational decisions regarding the next steps. To facilitate these processes, CHDR selects and develops biomarkers that can be used to show whether a compound is pharmacologically active. Ideally, biomarkers that have been measured in preclinical drug development are used in the earliest phases of clinical development. However, it should be noted that biomarkers measured in early drug development may not necessarily reflect the pathophysiology of the target disease. In healthy subjects, markers of pathophysiology are often not the easiest way to demonstrate pharmacological activity. For a good example of biomarker-driven early clinical development, see 'Moving the LPS challenge from test tubes to patients' on page 58.

Proof-of-principle for biosimilars

Now that existing patents on the first generation of biologic medical products are expiring, a growing number of so-called 'biosimilars' (also known as 'subsequent entry biotherapeutics') are being tested. These molecules are similar to the original products, but are produced by other companies using other cell clones and/or biological processes. Initial clinical studies with biosimilars often focus on measuring bioequivalence between the original product and the biosimilar (i.e. do these compounds have similar pharmacokinetics profiles?). The intended pharmacological effects of a biosimilar are usually investigated only in the target population, and the effects are assessed using clinical biomarkers. However, if a product fails in these later stages of clinical development, the consequences can be quite costly. Therefore, CHDR advocates the use of alternative biomarkers and/or bioassays in order to demonstrate pharmacological activity as early as possible.

Using biomarkers, CHDR investigates how a biosimilar compares to the original product in terms of pharmacokinetics, safety, and intended pharmacological activity. For example, a first-in-human biosimilar study was conducted at CHDR in 2015. Using *ex vivo* bioassays, researchers found that the biosimilar and original compound had equivalent pharmacological activity in healthy volunteers. Moreover, new insights were gained regarding the drug's mechanism of action. This knowledge may lead to more effective use of the drug, and it may pave the way towards identifying additional target conditions.

Unintended effects of biotherapeutics

In addition to demonstrating that a drug has the desired pharmacological effect, biomarkers can also be used to exclude the presence of undesired effects. For example, new biotherapeutics may trigger an unintended activation of the immune system, as biotherapeutics can contain trace amounts of immune-stimulating contaminants or may form aggregates, thereby causing toxicity in humans. If this occurs in an early stage of clinical testing, it can have serious consequences for the compound's further development. The challenge is therefore to identify the presence of unintended immune stimulation (e.g. due to contaminants, aggregates, or other avoidable problems) and/or responses that are due to the compound's pharmacological activity.

To determine whether and how new investigational compounds activate the immune system, CHDR has created a comprehensive panel of biomarkers and bioassays in collaboration with several research groups. This panel includes modified human cell lines that express reporter genes to measure activation of specific intracellular pathways. In parallel with this in vitro approach, the effects of biotherapeutics can be measured using *ex vivo* bioassays, which use samples obtained either from healthy subjects or from patients who were recruited via CHDR's extensive network of clinicians in a wide variety of fields. Whether the objective is to measure intended pharmacological effects or unintended effects, the goal remains the same: to provide the sponsor with reliable information that can be used to guide future decisions regarding clinical development.

Moving the LPS challenge from test tubes to patients

The challenge

How can we measure a compound's effects on inflammation?

Inflammation is a primary pathogenic pathway. Debilitating chronic diseases such as rheumatoid arthritis and Crohn's disease are inflammatory by nature, and inflammatory processes are also involved in atherosclerosis and psychiatric disorders such as depression. Given its widespread clinical relevance, new drugs are being developed to stop or slow one or more inflammatory pathways. For CHDR, the challenge is to demonstrate that a candidate anti-inflammatory drug has a pharmacological effect in healthy subjects. Because a drug that targets inflammatory pathways is not likely to have an effect in healthy subjects, a clever solution was needed. CHDR's solution was to develop a battery of in vitro tests designed to mimic various inflammatory processes in a test tube.

The solution

LPS: from test tube to subject

One of the key molecules in inflammation is TLR4 (Toll-like receptor 4), which was discovered by Nobel laureate Bruce Beutler. TLR4 is activated by the bacterial endotoxins lipopolysaccharides (LPS). The binding of LPS to TLR4 triggers the release of cytokines, eicosanoids, and nitric oxide, which in turn activate a variety of immune cells.

'We've been able to show that the *ex vivo* LPS challenge can be used to predict the anti-inflammatory effect of an investigational drug. We are now developing *ex vivo* challenges to address additional pathways in inflammation, as well as other processes such as cellular stress and fibrosis. Because interesting new developments are emerging in many fields, our goal is to establish a panel of robust *ex vivo* challenges to measure the pharmacological effects of these new compounds.'

CHDR uses LPS to trigger an inflammatory response, and in recent years this method has been developed as a tool for measuring the efficacy of anti-inflammatory compounds. The first step was to establish a reliable in vitro model using blood obtained from healthy subjects. Using this model, several key parameters were established, including the optimal LPS dose and incubation time. The relevance of this approach with respect to drug development became clear in a clinical trial using a new MAPK inhibitor: CHDR researchers found that the study compound had a clear pharmacological effect in healthy volunteers.

Of course, some may argue that activating blood cells in a test tube is too far removed from measuring an inflammatory response in humans. Importantly, many cell types involved in inflammation – for example, endothelial cells and hepatic cells – are not included in the model. Therefore, CHDR took the next step and developed an LPS challenge for use in human subjects. However, because LPS can also activate systemic cytokine responses, which play a role in sepsis and other severe conditions, caution is needed. Even at relatively low doses, LPS can cause fever and malaise. Building on published LPS data, researchers found a dose that causes relatively mild symptoms yet triggers a measurable inflammatory response.

In the past year, CHDR has further characterised the *in vivo* LPS challenge model, as well as measuring the effects of LPS on the vasculature (by measuring activation markers in endothelial cells and platelets) and in the kidneys. These studies revealed that the *in vivo* LPS challenge is a relevant model for assessing the anti-inflammatory effects of investigational drugs in early stages of development; in addition, this model can be used to examine the effects of new drugs aimed at protecting tissues and/or blood vessels.

Results

The *ex vivo* assay is equivalent to performing *in vivo* testing in human subjects

The activity of an anti-inflammatory monoclonal antibody was measured in a comprehensive study using the above-mentioned *ex vivo* and *in vivo* LPS challenges in healthy subjects. The results confirmed that the *ex vivo* assay is suitable for quantifying the antibody's pharmacological activity, revealing that the antibody's anti-inflammatory effect was similar between *ex vivo* and in vitro challenges with respect to both magnitude and duration.

Conclusions

The *ex vivo* challenge is an extremely robust tool for measuring a drug's pharmacological effect on a specific pathway.

‘CHDR provides more than just medical expertise’

Their ability to combine outstanding science with highly effective study execution makes CHDR unique. They go far beyond simply providing medical and research expertise; they bring in people who are highly motivated, invested in the project, and top-notch researchers. This approach is quite different from most other CROs. Because CHDR is a non-profit foundation, they can focus on delivering high-quality research, including cutting-edge technology and implementation.

VP of Clinical Operations
Biotech company*

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

Education: a core value at CHDR

Contributing to the education of both students and professionals has always been one of CHDR's guiding principles, and 2015 was no exception. CHDR's vision of education is that it should be innovative, technology-driven, and inextricably linked with research. In other words, education is one of the ways in which CHDR expresses its own identity.

Each year, CHDR staff members give more than 200 lecture hours to medical students at Leiden University Medical Centre (LUMC). In addition, our staff members present workshops and seminars to biomedical science and biopharmaceutical science students at Leiden University. These programmes are extremely popular, and the number of participating students has risen steadily through the years. For example, in the biopharmaceutical sciences, nearly 300 students started in 2015 compared to fewer than 100 students in 2010. Given this trend, it is highly likely that the demand for education in pharmacology will continue to grow, particularly now that LUMC recently established a new Pharmacy programme.

These numbers reflect the need for innovative – and even radically ground-breaking – approaches to education. Most lectures are essentially the same each year, giving even the most motivated educators an experience reminiscent of the movie 'Groundhog Day'. Future physicians, pharmacists, and scientists need more than just information; they also need to know how to apply knowledge in practical situations. Thus, they need to bridge what they learn with real-world situations. To help build this bridge, a special project devoted to 'e-learning' has been established in order to take stock of what resources are available and to identify which additional materials need to be produced. In this project, CHDR will collaborate closely with partners at Leiden University and LUMC, so that in coming years, a combination of online content, apps, books, lectures, and workshops will help future professionals prepare for the unique challenges they will face. For example, in some cases a massive open online course (MOOC) may replace a lecture. In other cases, a more intensive approach may be needed, such as the Frontiers of Science course in Clinical Pharmacology. And with CHDR's Teaching Resource Centre (see below), students at universities around the globe can reap the benefits of new e-learning resources as they become available.

Teaching Resource Centre

One of CHDR's major contributions to the education of students worldwide is our free app called TRC (Teaching Resource Centre). Users who install this app on his/her smartphone gain instant access to a user-friendly virtual pharmacology textbook. To date, the TRC app has been downloaded more than 130,000 times by students throughout Europe, the United States, and many other countries, including developing countries. Until this year, the TRC app had a major limitation: it lacked a reference drug formulary that could be used by US students and practitioners. For Dutch students and physicians – and their British counterparts – the app includes an interface with the main pharmacotherapy formulary (the Farmacotherapeutisch Kompas in the Netherlands and the British National Formulary in the UK). In the US, however, this formulary is available only to students and physicians who pay a subscription fee.

Thanks to a fruitful collaboration with the University of Iowa Medical School, the TRC app now includes a connection to Micromedex Ltd., one of the largest companies offering pharmacotherapeutics guidelines to 4500 university hospitals and general hospitals around the world. Now a student at a university that subscribes to Micromedex can use the TRC and can automatically access the Micromedex database using IP-gated authorisation. Adapting the TRC to this new resource was no minor operation: 721 web links had to be checked manually. But the end result was worth the effort, and the new TRC app is even more useful.

Teaching professionals

CHDR is also actively involved in postgraduate education. For example, physicians and pharmacologists who wish to specialise in pharmacotherapy or drug-related clinical studies can be trained as clinical pharmacologists. The programme can be completed in one year, or it can spread over several years. The curriculum includes courses and practical training in a variety of topics, including how to design and conduct pharmacology studies in healthy subjects and patients, clinical work, and advising physicians regarding the choice, dosage, adverse effects, and interactions of drugs. Importantly, training medical specialists in clinical pharmacology has helped CHDR's network grow.

In addition to clinical training, CHDR also trains researchers who wish to become entrepreneurs in the biotech industry. Oftentimes, young scientists who wish to bring their new ideas to market are forced to learn the 'secrets' of business the hard way. In the past, no formal training was available for scientists who wanted to become an entrepreneur. But now, there is FutureLab, a postgraduate training programme for aspiring entrepreneurs and future leaders in the life sciences and healthcare fields. In this programme, cases are discussed in order to help trainees learn about the various roles that a scientist/entrepreneur needs to perform in order to be successful.

With these education programmes, CHDR contributes to developing more rational and balanced approaches to drug development and pharmacotherapy, while keeping an eye on the ethical and social implications of these activities.

An intensive programme for training highly talented clinical researchers

In 2015, CHDR's Human Resources department developed the Clinical Research Programme to help talented junior clinical scientists with their career development. The programme, which started in early 2016, offers a well-defined development path for ambitious young researchers and physicians at CHDR.

CHDR's innovative approach and high level of scientific expertise are due in part to its many talented junior researchers. The Clinical Research Programme was developed specifically to offer scientific and personal development in a formal, structured setting.

In this intensive five-year programme, participants conduct several research projects while being coached by senior clinical scientists and research directors. The participant is responsible for developing, leading, and reporting a clinical trial, thereby gaining expertise in a specific scientific field. Importantly, the outcomes of the study are can be included in the participant's PhD thesis.

Selection and coaching

Interested applicants can learn more about the Clinical Research programme through CHDR's career website. Applicants then perform an online evaluation and are interviewed by several staff members. If the candidate is selected, he/she is assigned a 'coach', usually a clinical researcher with at least four years of experience at CHDR. The coach guides the participant during the first year of the programme. In addition, a senior project leader supervises the participant on a daily basis throughout the programme. All participants meet formally with a research director three times a year in order to discuss the participant's personal and scientific development and to establish the next set of scientific and management goals. Annual performance evaluations, combined with '360-degree' assessments in the first and fifth years of the programme, provide the participant with valuable feedback and ensure a tailored learning experience for optimal talent development.

The 5-year programme at a glance

Throughout the five-year programme, participants develop key skills and competences, including project management, clinical pharmacology, scientific research, and personal competences. Participants also collect data for their PhD thesis, which they are expected to complete during the programme.

After the programme

In the final year of the programme, the senior project leader discusses the participant's future plans. If the participant is a suitable candidate, and if a position is available, the participant may be invited to join the staff at CHDR. Whether the participant remains at CHDR or seeks employment elsewhere, his/her newly establish skills and competences will help ensure success in the fields of research, business, and/or healthcare.

Highlights

A hands-on approach to teaching clinical pharmacology

The challenge

How can we teach Master's students to design studies in clinical pharmacology?

Together with the LUMC pharmacy, CHDR offers a course in study design to Master's students in biomedical sciences. In the past, this course was largely theoretical, teaching students the dos and don'ts of clinical pharmacology research. Unfortunately, students can learn only so much with this approach. A more practical, hands-on course can have a much greater impact. But what can be achieved realistically in just three weeks' time?

The solution

Three intensive weeks of interactive, hands-on learning

In 2015, this course was revised considerably to make optimum use of the three weeks. The first change was to have the students design a study themselves. The instructions were to design a study to measure the effects of the well-known beta-blocker metoprolol. The students were challenged to consider various aspects of pharmacokinetics and pharmacodynamics, including pharmacogenetics (the effect of genetics on metabolism). The rate at which metoprolol is metabolised by the liver is influenced by genetic factors; some people metabolise the drug slowly, some metabolise the drug extremely rapidly, and the majority of people are somewhere in the middle.

In the second week, each student could choose to be either a subject or an investigator in the clinical pharmacology trial using metoprolol. The protocol had been previously written and was approved by the ethics committee. Metoprolol is a widely used drug with extremely high safety, particularly in healthy young adults. Still, ethics committee approval was critical, as young adults are considered to be a vulnerable population, particularly if the study is performed in the context of their education. For example, a student should be free to refuse to participate without fear of academic consequences.

The randomised, double-blind, placebo-controlled study was conducted at CHDR and lasted two full days. A variety of measurements were collected, including blood pressure, ECG, and blood samples to measure obtain pharmacokinetics and pharmacogenetics profiles, which were used to determine each subject's rate of metoprolol metabolism.

In the third week of the course, the students analysed all of the data obtained during the study, and they evaluated the entire process. The students focused on the most important data, discussing various aspects of pharmacokinetics and pharmacodynamics. Of course, a comprehensive analysis would have required more time. Generally, performing such a study, including data analysis, can take eight weeks or longer. But the data didn't go to waste: a more detailed analysis of all of the results, including the pharmacogenetics, was performed later by biopharmaceutical sciences students during their internship at CHDR.

Results

An intensive, hands-on educational experience for everyone involved

The students were extremely positive about this newly designed programme. Importantly, the outcome was meaningful because the course mimicked the real-life situation. For example, one subject was not eligible after medical screening, and another subject dropped out during the study. To the instructors, it was clear that the students had learned new things in a way that made it easy to both implement and remember. For example, when designing the study the students wanted to collect as many blood samples and data points as possible. But when performing the actual study and analysing the data, they quickly realised that more measurements and samples increased their workload exponentially. And obtaining more blood samples added to the burden placed on the subjects (i.e. their fellow students). In short, this hands-on approach can be considered a success.

For both the LUMC Pharmacy and CHDR, this course was quite an investment, particularly given that all other clinical activities had to continue as usual. The timelines were almost too short to be feasible, but thanks to the enthusiasm of the staff members, things went quite smoothly. This course will be repeated in 2016.

Conclusions

Using a hands-on approach to teach students clinical pharmacology is far more rewarding – and far more effective – than teaching in a traditional classroom setting.

'It was an intense experience for everyone, including the staff at CHDR and the LUMC pharmacy, who had to put in extra hours to perform the study in such a short time. But it was also clearly worth the investment, and it was inspiring to see how much the students learned using this approach. This network of academic and professional partners is unique and helps position CHDR as a global leader in clinical pharmacology education.'

Working with CHDR

‘Very good at responding to feedback’

CHDR is a very science-focused organisation with high operational efficiency. CHDR is particularly good at listening to feedback from sponsors and then acting upon it. In addition to being highly responsive, they also provide valuable feedback. I recommend CHDR to any research organisation that’s looking for a CRO that goes above and beyond standard research.

Alliance Leader
Top 10 Big Pharma Company*

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

Working at CHDR

Carmen van der Does

Clinical research unit administrator

Tonight, another study is scheduled to begin. This means that we need to make sure everything is in place. For example, the blood collection tubes need to be properly labelled to minimise chances of a mix-up. It's my job to pick the right person for each task, coach them, and check their work. Of course, I always try to take into account what a person likes best.

Before each study, we prepare everything, starting with appointments for screening the subjects. It's important that everything runs smoothly, and the project leaders and staff depend on us for that. I also like the energetic atmosphere here at CHDR.

'Working at CHDR is dynamic and always full of variety'

When I first came to CHDR, I did a variety of jobs, and then I was promoted to a team leader. Another positive aspect here is the mixture of regular staff and temporary employees. Of course, this also means that we need clear, well-documented procedures so that new employees learn quickly. It's always dynamic, and I like that.

Ingrid de Visser

Senior project leader

An important part of my job is coaching project leaders, and my door is always open. I would prefer to have someone ask the same question ten times rather than making even one mistake. Another key aspect is assigning the right project leader to a given project by taking their scientific and personal interests into consideration. For some projects (for example, when we conduct a trial at an external location), special experience may be needed. I particularly enjoy the challenges, the high scientific standards, and the attention to detail.

In this respect, no two days are ever the same. The growth of our organisation means that we need to work in a more formal environment, with everything thoroughly documented. But at the same time, CHDR is still informal and relaxed, so people feel free to speak their mind. And working in our new building is simply fantastic. The building is designed with research in mind, and it reflects the transparency of our organisation. So when I talk with sponsors, I don't have to tell them; they can see it with their own eyes.

Rob Zuiker

Senior project leader

My job has many exciting aspects. I coach the project leaders, coordinate, prepare, and execute trials, and I evaluate the trials with the sponsors. Our work combines clinical skills and science with management and education, so it's always new. The average time for a trial – from the initial planning stage until the final evaluation – is approximately nine months. After one trial finishes, we start anew, with a new compound, new format tailor-made for the next trial, and new challenges; that's what I find particularly fascinating. As you can tell, I like my job, and I like CHDR and its culture.

At CHDR, everyone's extremely dedicated. Sometimes, you're part of something that might be revolutionary, like measuring the effects of benzodiazepines on driving performance using a driving simulator. This is an approach that we pioneered, building on our research director's experience studying cognitive performance in subjects after taking a benzodiazepine. Working with professionals who have so much experience and so many creative ideas is extremely inspiring.

Christophe Mombers

Intern

During my Master's study in Biopharmaceutical Sciences, I was fortunate to do my internship at CHDR. In my 12-month internship, I learned so much and contributed meaningfully. For example, I was at the forefront of innovation, testing wearable sensors for CHDR's Trial@Home. These sensors may look like simple patches, but they measure temperature, single lead ECG, body movement, and more. Using those measurements, you can also extrapolate other parameters such as respiratory rate and energy expenditure. The sensors connect to a cell phone or iPad via Bluetooth, so we can monitor subjects as they go about their daily business. It was really exciting to contribute to this new technology. I particularly like the sense of openness here at CHDR. For example, you can approach anyone, and they are happy to take the time to answeryour questions.

'I particularly like the sense of openness here'

The discussions at meetings are also extremely open, without the rigid hierarchy you often see in academic and hospital settings. I hope to come back and work here someday.

Liesbeth Houweling
Data manager

In the Data Management group, we are involved from the beginning of a study through to the end. When the protocol is ready and the project leader starts to create the database, we ensure that everything is feasible for the nurses and that the data will be compatible with our own database and with the client's database.

I started working as a nurse at CHDR nearly 15 years ago. After six years, I was ready for a new challenge, and I was glad to get the opportunity to become a data manager. In fact, that's one of the things I like about CHDR: they take good care of you. I've always been interested in the scientific research process, particularly the combination of medical information and administrative data. That makes it easier to understand things and to ask the right questions if something doesn't make sense in the data. In my time at CHDR, many things have changed. These days, for example, nurses enter most of the data directly into the database using dedicated iPads. And sponsors often expect the completed dataset within as little as a week. And despite our experience, we are a 'young' company in the sense that many young, energetic people work here. That creates a dynamic atmosphere here.

Jelle van Hasselt
Data entry officer

My first experience with CHDR was as a student, first as a test subject and later as a test assistant. My work as a test assistant was a particularly useful experience. Later, I really wanted to work here, and I was fortunate to land this job. In the data entry group, we are involved in the entire process, from setting up the database for a new study to the final transfer of the data to the sponsor. Throughout the process, we verify the data, send out queries when something is not clear, host our sponsors' monitors, and much more. It's very diverse. And because data collection is at the core of what we do at CHDR, I'm in touch with almost everyone here. What I like about CHDR is the atmosphere, which is open and informal, yet still very professional. For me, it's always a matter of pride showing someone around the facility.

Casper Kortmann
Screening physician

I started working here soon after completing my medical training. What I really like is the large amount of time I can spend with each subject, about half an hour. The screening process itself is always different, as each study has its own set of inclusion and exclusion criteria. And you have to be careful not to miss subtle yet important issues such as a heart murmur. From a medical perspective, it can be quite rewarding work, as most of the subjects I screen are either healthy young people or patients with specific medical issues suited to a specific study. Above all, I like my colleagues, the atmosphere, and the opportunities. For example, I wanted to organise a holiday party for everyone at CHDR, and I didn't have to ask twice. And if I have suggestions regarding the questionnaires we use, I know they'll be heard.

Sabine Deferme
Team leader, Nursing staff

This is the perfect job for me. I just love to organise, coordinate, and plan, and that's what I get to do every day. It's our job to ensure that each study has sufficient nursing staff available. Planning involves many other things as well, often involving several studies simultaneously. We start planning quite early in the process, as soon as the protocol is approved. Even so, we need to expect the unexpected, for example if a nurse becomes ill or if a study needs to be postponed for some reason. My motto is, 'Everything is possible.' So if a challenge arises, I'm ready to take it on.

'Everything is possible'

I also like the diversity: the differences between studies and the changes in the organisation through the years. And despite all of the growth in the past few years, CHDR still has a strong sense of community. We're in this together, and we recognise and value each other's contributions to our continued success.

Herbert Anholts
Recruitment manager

I have a commercial background, so I like to contribute my enterprising spirit. Recruiting subjects has become a greater challenge now that we need so many subjects for our studies. It is no longer sufficient to be well-known among students . Part of the challenge is that our recruiting strategy must meet strict ethical criteria. For example, subjects cannot be attracted using financial compensation; the subject must want to participate for altruistic reasons, for example to help medical science move forward, not simply to get money for a ski vacation. Still, we've been extremely successful at finding healthy subjects and patients for specific studies. That's quite a rush, I can tell you. And sometimes, you really have to go the extra mile. For example, I remember when we needed Japanese subjects for a study on alcohol. Because the Netherlands has a relatively small Japanese population, finding suitable volunteers was quite a challenge. So we visited all of the sushi bars and restaurants in Amsterdam, and we found enough participants!

'We have a good team, and everyone is willing to help each other'

The other reason I really enjoy working at CHDR is that we have a good team, and everyone is willing to help each other. I couldn't do my job without them. And I like the way CHDR cares for its staff. For example, when someone is ill or has a personal issue, everyone takes an interest. That's the kind of organisation I like to work for, and that's why I've been with CHDR for more than ten years.

‘A research partner, not just a vendor’

When we first started working with CHDR, we viewed them as a vendor. But as we saw how they work, their valuable input, and their ability to take control of the situation, we realised that they would be better suited as a partner. CHDR is a unique CRO: because they are a non-profit organisation, their revenue is channeled back into research and training. We appreciate this commitment to helping move science forward. CHDR employs researchers with the training and dedication needed to successfully perform early-phase, high-quality experiments using methodologies that must first be established and validated. Very few CROs have the level of professionalism and motivation that CHDR possesses. CHDR’s mindset is clear: Tell us what you’re after, and we’ll help you find the right solution.

Vice-President of Experimental Medicine
at Big Biotech*

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

Volunteering at CHDR

Study participants discuss their experiences at CHDR

In 2015, 1277 subjects spent a total of 15615 days and nights at the CHDR facility. To find out what it's like to participate in a study with CHDR, we sat down with some of our volunteers.

'Interesting, and quite intensive.' That's how Harry K* describes his experience as a participant in a study of a new drug for Alzheimer's disease. 'We did a lot of tests, and we got to wear a special cap that measured our brain activity. They really kept us busy.'

Jacob L, a medical student, had quite a different experience. 'I had plenty of time to read, study, and relax. I was glad to use the time to prepare for my exams.'

Maxine J, who volunteered for two studies, understands that the experience depends largely on the drug being tested. 'Sometimes, all they need to measure is your temperature and blood pressure. But with other drugs, you may have to do all kinds of tests. I find the variety really interesting.'

Three experiences

Harry spent a total of ten days at the facility. 'I was there five times, for two days at a stretch. And before that, I attended an information session and a screening session. After the first visit, CHDR paid for all of my expenses. I liked that detail. As I said, I found the tests really interesting, and overall it was a positive experience.'

Jacob was at CHDR a total of 19 days. 'For me, the length of the study was perfect. I'd had quite a stressful year, so this was like a little vacation. Aside from one day in which we had to lie down the entire day, the rest of the study was relaxed and routine. I woke up – I was really happy to have a private room given how long the study lasted – ate breakfast, took the medication, and was then free to spend the rest of the day as I wanted. We just had to have our blood pressure measured a few times each day. The meals were good, the facilities were excellent, and I had a lot in common with the other participants. So even though I was participating in a drug trial, I enjoyed myself, too.'

Maxine participated in two trials. 'The first trial was conducted in November 2014. This study included four sessions, two days and two nights. During the study, I received an infusion of a drug designed to help patients with Alzheimer's disease. There were no tests I had to perform; they just measured my temperature, pulse, and blood pressure. In December 2015, I participated in a trial to study a new sleep-aid medication. In this study, I performed all kinds of tests using a computer, so they could measure the effects of the medication.'

Friendly

These three participants came from different backgrounds, and they participated in strikingly different studies. Nevertheless, their stories have several striking similarities. Harry: 'I liked the conversations I had with the research assistants, most of whom were medical students. They were really friendly and open. And I enjoyed hearing their stories, for example, how they learned to sew sutures in order to practise their surgical skills.' Maxine: 'I give them the highest grade. They're so nice.' Jacob agrees, but then he knew many of the research assistants from medical school. 'I also know many people who participate in drug trials at various facilities. Unlike other companies, CHDR treated us like adults. They didn't chase after us to make sure we'd be on time for a measurement; they just told us to be there at a certain time, and we were.'

For all three participants, financial compensation was not the primary reason for participating. Harry wanted to help with progress in medical science. 'I hope they can use my results. Maybe I'll volunteer again, even though there's always a slight risk involved. Personally, I don't mind; after all, if you read all the possible side effects associated with any drug, you'd never take anything.'

Jacob wanted to experience first-hand how new drugs are tested; when he becomes a doctor, he'll prescribe them. 'I wanted to learn as much as possible about the drug trial, the compound, the entire process. I found it extremely interesting. If I have time, I'd like to participate in another study.'

'I'd had quite a stressful year, so this was like a little vacation. There was one day that was really intense, when we had to lie down all day, but all the others were a relaxed routine.'

For Maxine, her motivation for volunteering is to help others. 'I've also been a blood donor for forty years. I'm retired, and luckily I don't take any medications. So whenever they need healthy people my age, I'm happy to participate. Of course, for your safety you can only participate in two studies each year, which is good. I'll be happy to participate in another trial at CHDR.'

** To protect their privacy, the names have been changed.*

Working with CHDR

‘Top-notch scientific support and subject recruitment’

In a clinical trial, the most important elements are medical and scientific support and ensuring the safety of the participants. In all of these aspects, CHDR meets our full expectations.

Head of Clinical Pharmacology
Top 50 Pharma Company*

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

Scientific output

Bibliometric analysis CHDR 2015

As in previous years, CHDR performed a bibliometric analysis for 2015. This analysis enables us to evaluate CHDR's publication record and impact, and we can compare our performance with previous years and benchmark institutes.

It should be noted that finding benchmark institutes for this bibliometric analysis is challenging, as CHDR is not a conventional CRO and is highly active in clinical pharmacology training, education, and publishing. Thus, we used academic research institutes that specialise in clinical pharmacology as our primary benchmarks (Table 1).

Publication output

Many research activities can be quantified in order to measure output; however, one of the most commonly measured activities is the number of journal publications. Note that the number of publications in a given year can only be measured in the following year; therefore, research output is provided through 2014.

CHDR's publication record has increased steadily since 2009. This increased number of publications is partially a reflection of CHDR's growth, as each successive year, CHDR performs more clinical studies. CHDR's output is on par with the benchmark institutes LUMC, Heidelberg, and Radboud.

Ranking performance in terms of absolute numbers of papers published helps us measure CHDR's output against other institutes. However, this bibliometric does not take into account the number of researchers at each institute. Because the number of researchers varies among benchmarks, comparing the impact of the publications may be more appropriate. Table 2 summarises the various indicators of impact that we can measure.

Benchmark institutes

PRA	PRA International, Zuidlaren , the Netherlands
Edinburgh	BHF Centre for Cardiovascular Science, Edinburghh: Pharmacology, Toxicology & Therapeutics, Scotland
Heidelberg	Heidelberg: Clinical Pharmacology and Pharmacoepidemiology, Germany
LUMC	Leiden University Medical Centre: Clinical Pharmacy and Toxicology, the Netherlands
Radboud	Nijmegen St. Radboud: Pharmacology and Toxicology, the Netherlands
UMCG	University Medical Centre Groningen: Clinical Pharmacology, the Netherlands

Citation impact

Citations are references to previously published articles, including primary research papers and review articles. Tracking citations provides a robust measure of the impact of published research. The indicator Mean Normalised Citation Score (MNCS) is used to measure an institute's citation impact; this indicator provides the normalized number of impact citations over a 4-year window (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 2014. A normalised citation score of 1.0 indicates that the number of citations matches the average number of publications in the field.

CHDR's MNCS has increased since 2010 and is currently on par with the global.

The bubble plot on page 91 shows each institute's publications as a percentage of the entire oeuvre and the corresponding number of citations. This plot shows that CHDR's citation impact is on par with our benchmark institutes.

PP (top 10%)

PP (top 10%) provides a measure of the proportion of publications in the top 10% of highly cited papers. A value >10% indicates a relatively high proportion of highly cited papers. PP (top 10%) is affected less by outliers than MNCS; with sufficiently high output, an individual publication will have relatively little effect on the results.

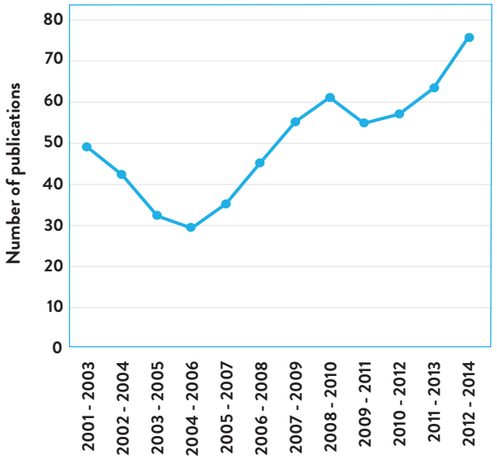
Journal impact

Mean Normalised Journal Score (MNJS) represents the impact of a scientific journal. Generally, MNJS is used to measure the relative importance of a given journal within its field, as journals with a higher impact factors are considered more relevant to the field.

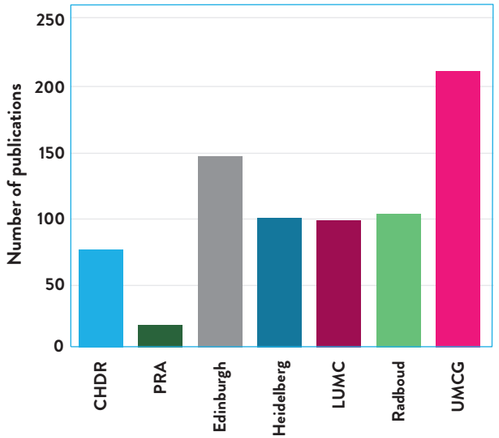
Overview of publication indicators

Indicator	Dimension	Definition
P	Output	Total publications
MNCS	Impact	Average normalised number of citations to the publications
PP (top 10%)	Impact	Proportion of papers in the top 10% of the respective field.
MNJS	Journal impact	Average normalised citation score of the journals

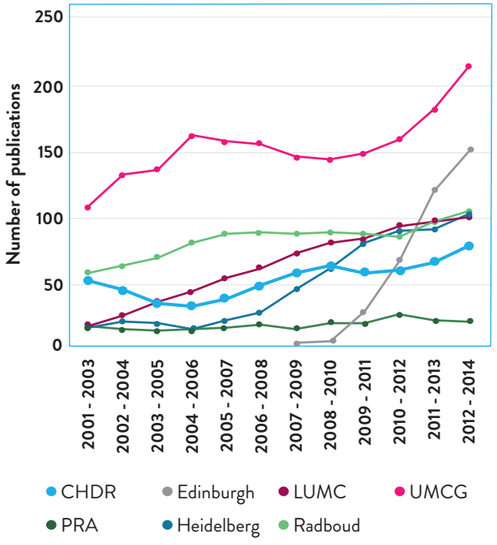
Number of publications by CHDR in 3-year intervals from 2001 through 2014



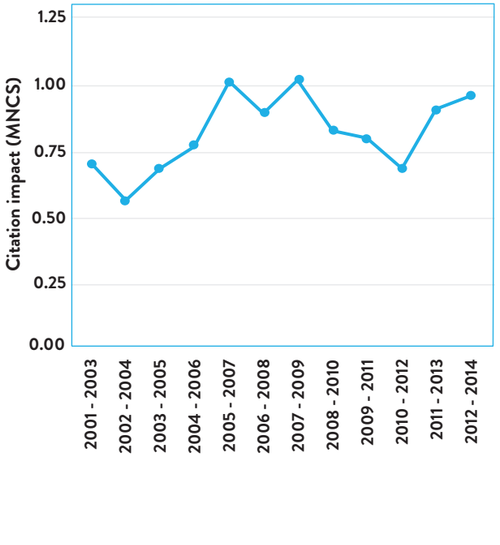
Number of publications of CHDR and benchmark institutes from 2012 through 2014



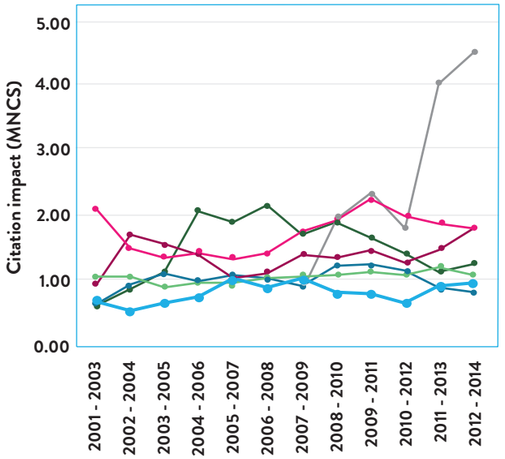
Number of publications by CHDR and benchmark institutes from 2001 through 2014



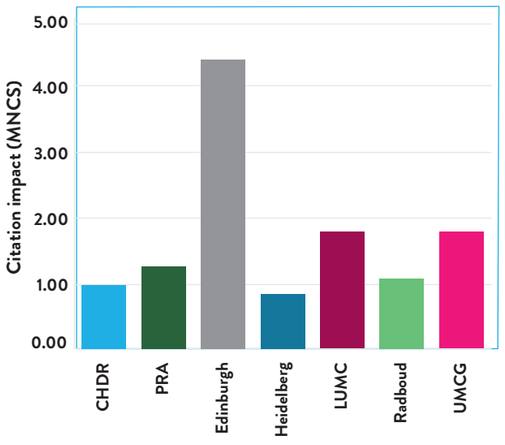
Citation impact of CHDR from 2001 through 2014



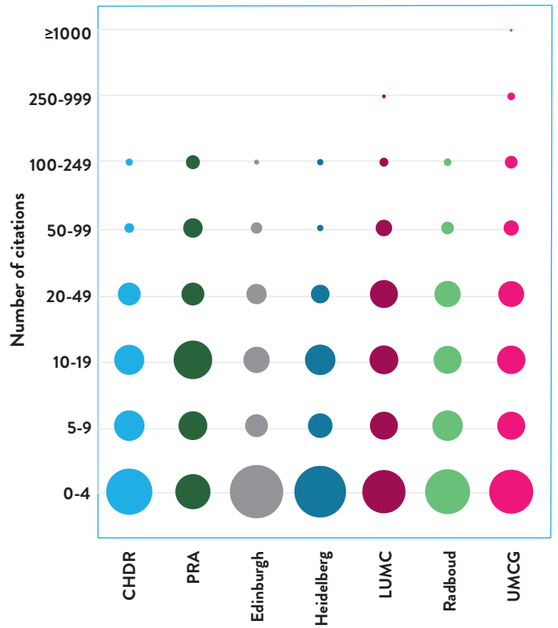
Citation impact of CHDR and benchmark institutes from 2012 through 2014



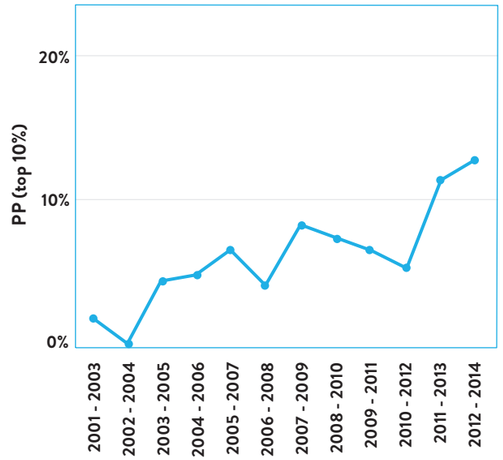
Citation impact of CHDR and benchmark institutes institutes from 2012 through 2014



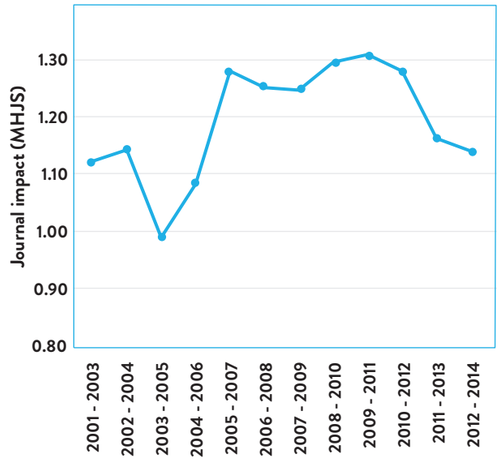
Bubble plot of citation impact. The bubbles represent the publications by CHDR and benchmark institutes as a percentage of the entire oeuvre (x-axis) and the citation frequency (y-axis) for 2001 through 2014



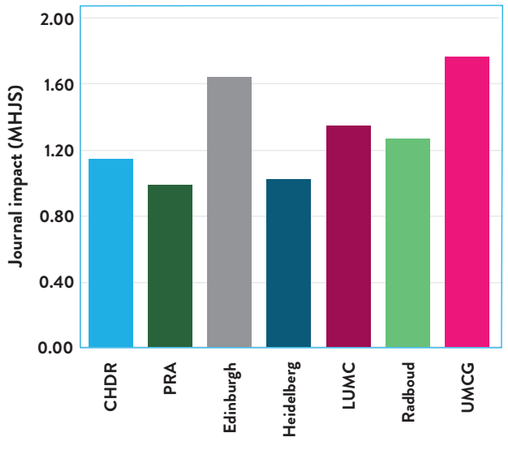
Proportion of high-impact papers by CHDR from 2012 through 2014



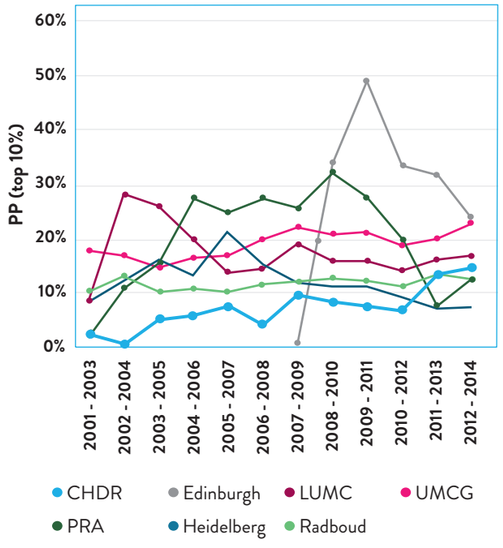
Journal citation impact of CHDR from 2012 through 2014



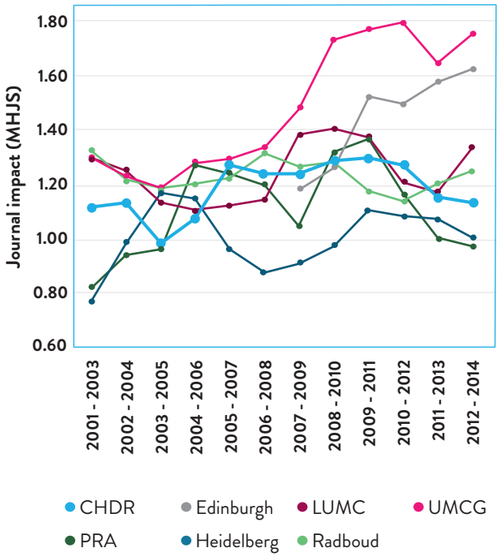
Journal citation impact of CHDR and benchmark institutes from 2012 through 2014



Proportion of high-impact papers by CHDR and benchmark institutes from 2012 through 2014



Journal citation impact of CHDR and benchmark institutes from 2012 through 2014

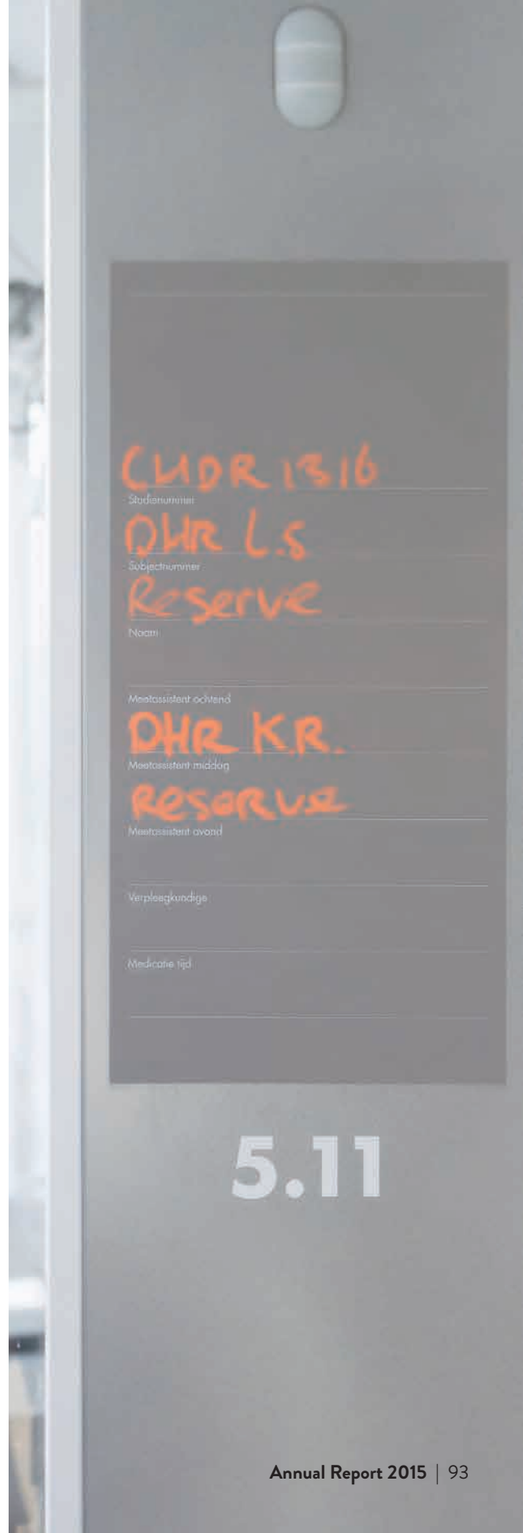


Conclusions

CHDR's recent growth is reflected nicely in CHDR's research output: both have increased since 2009. Importantly, both the number of publications and the impact of those publications have increased.

Although CHDR's journal impact decreased slightly compared to previous years, CHDR publishes regularly in higher-impact journals. Currently, 15% of CHDR's publications are in the top 10% of publications in their respective fields.

Because CHDR is unique in the field, focusing on both research and education, finding the best benchmarks can be difficult. However, although most of the benchmark institutes in this analysis are academic centres that focus on research publications, our analysis shows that CHDR has performed well through the years.



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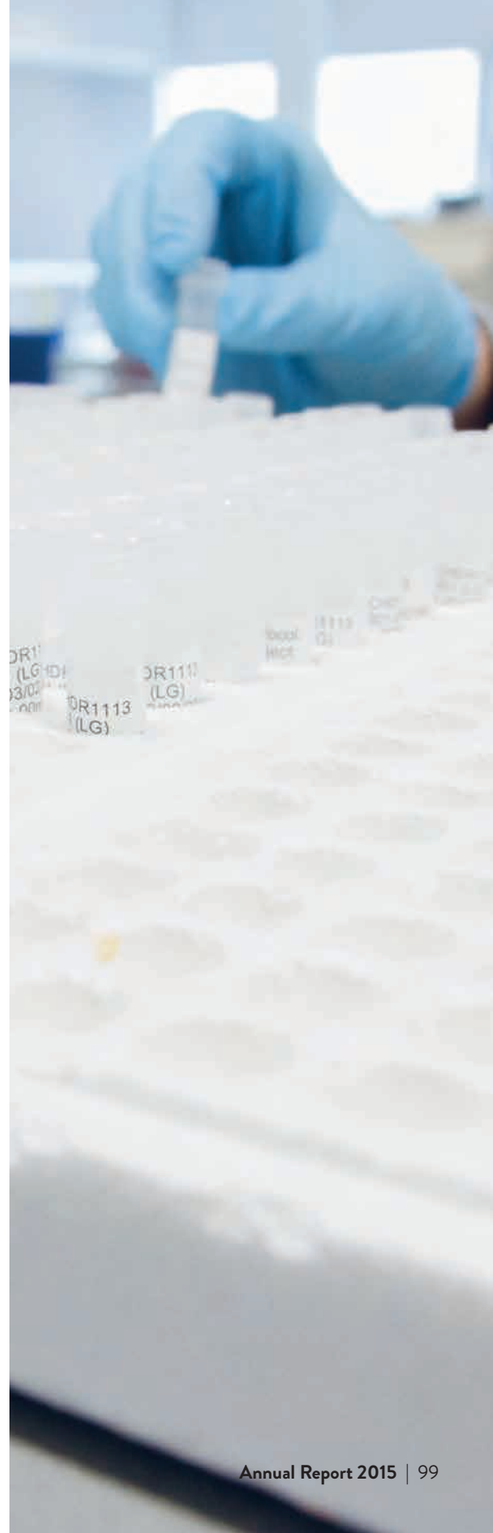


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