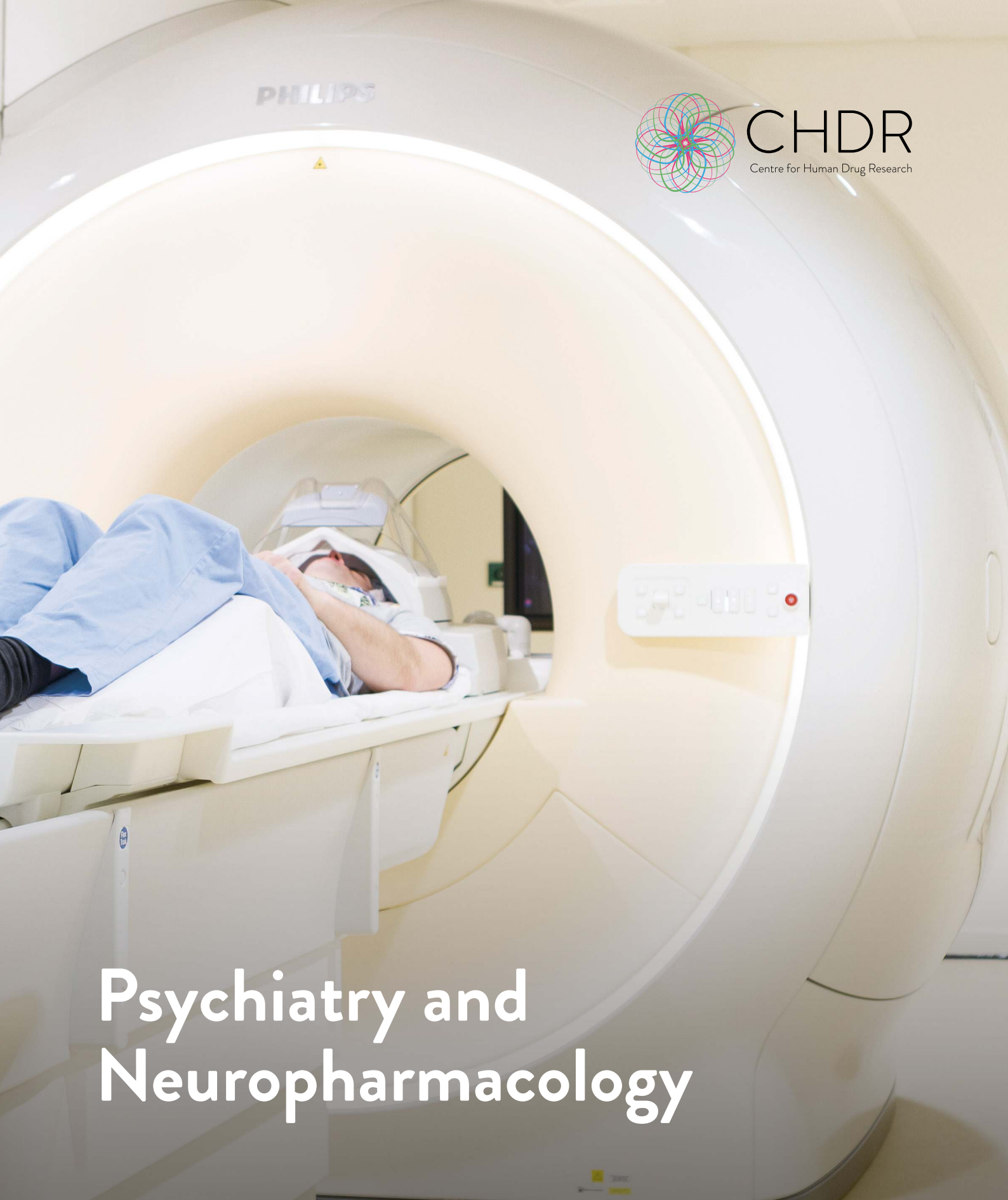


CHDR
Centre for Human Drug Research

Psychiatry and Neuropharmacology

Neurophysiology and psychiatric symptoms

At CHDR, our long history of research allows our investigators to take a combined neurophysiological and phenomenological approach to developing psychiatric compounds. A powerful example of this approach is NeuroCart®, which is used to characterise the pharmacological effects of compounds on a wide range of neurophysiological and neuropsychological functions in both healthy subjects and patients. NeuroCart can also be used to measure functional diagnostic processes in psychopathology. In addition, CHDR has a highly effective recruitment strategy, allowing researchers to recruit patient cohorts with a various psychiatric conditions. Importantly, in studies involving psychiatric patients, CHDR collaborates closely with the patients' own healthcare professionals in order to ensure continuity of care.

Practical answers to important research questions

Does our compound have the desired effect?

Our combined approach allows CHDR researchers to assess whether novel compounds have the desired effect on CNS function. For example, to study a selective new GABAA α2α3 receptor agonist developed for treating anxiety disorders, CHDR researchers used NeuroCart® and found that the compound likely has anxiolytic effects in patients.

What is the optimal dose for testing our compound in patients?

Continuing the example above, the results of our early-stage clinical studies enabled us to determine the optimal pharmacologically active dose for future trials in patients with anxiety disorders.

CHDR has also played a central role in developing a rapidly dissociating dopamine receptor D2 antagonist. Researchers used a NeuroCart® test to measure D2 receptor antagonism, thereby estimating the optimal oral dose for maximum D2 receptor occupancy.

‘Using pharmacological challenges relevant to psychiatric disease, we can demonstrate in healthy subjects that the compound will likely affect specific systems. In patient studies, this approach allows us to identify the patients in which the compound will have the highest likelihood of exerting a therapeutic effect.’

Psychiatry and neuropharmacology highlights

- CHDR has extensive experience testing novel CNS compounds in early-phase clinical trials involving both healthy volunteers and patients;
- NeuroCart®, a comprehensive neurological and psychological test battery developed at CHDR, is used to link pharmacological mechanisms to relevant functional CNS domains;
- Validated pharmacological challenge tests can be used to demonstrate specific CNS effects in healthy subjects;
- Additional applications include neuroimaging techniques such as resting-state functional magnetic resonance imaging (rs-fMRI) and positron emission tomography (PET), which are used to confirm that the relevant targets and/or networks are reached.

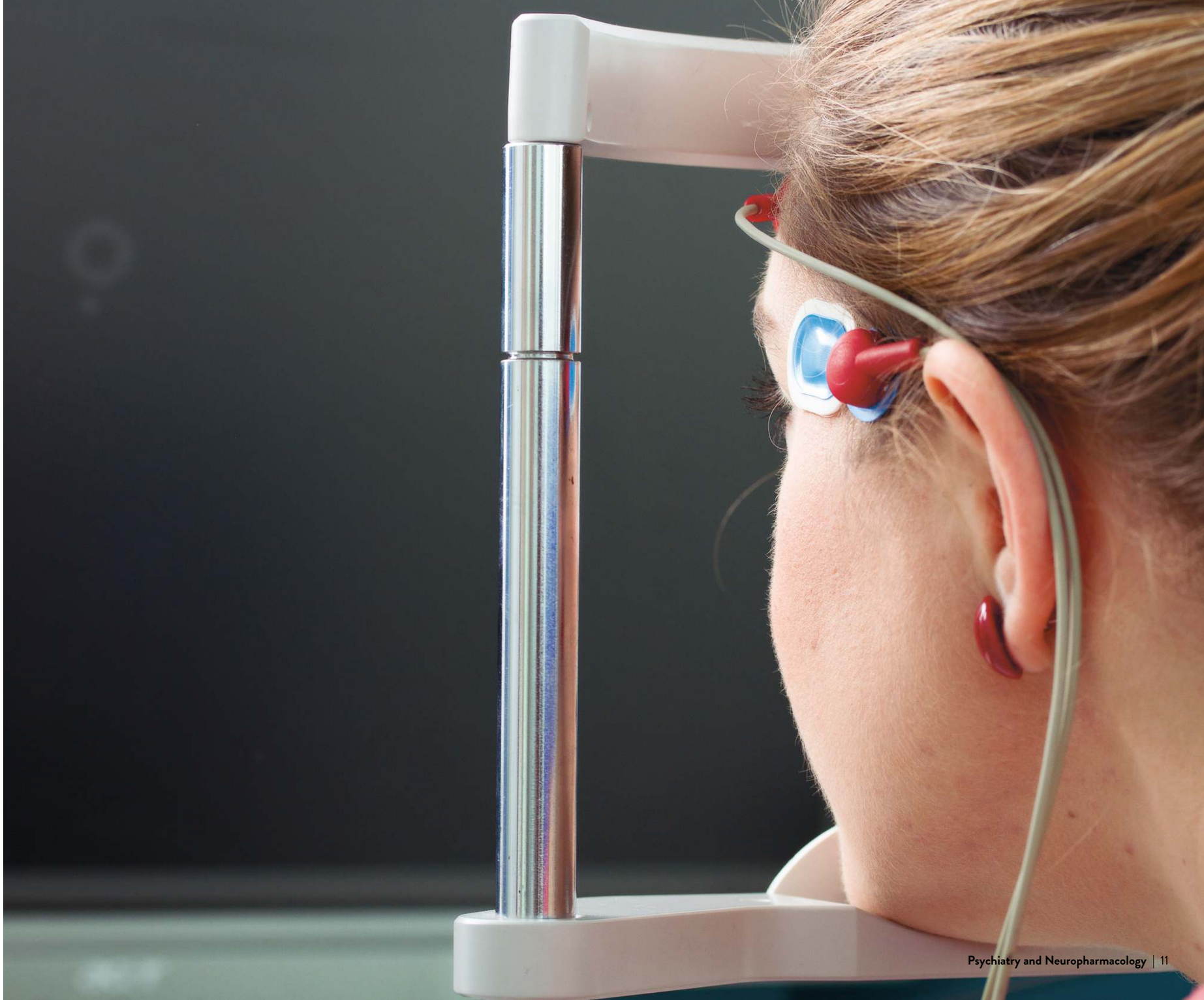
Psychiatry and neuro-pharmacology: a closer look

Why is drug development such a challenge in the field of psychiatry?

The field of psychiatry currently has a high demand for more effective, faster-acting drugs with minimal side effects. However, each step required in developing a new psychiatric drug is more challenging than the same respective steps in most other medical fields. Preclinical psychiatric drug research is severely hampered by a lack of relevant animal models that recapitulate the polygenetic, neurobiological, and psychosocial aspects of most psychiatric diseases. In addition, early clinical trials in healthy subjects rarely address the compound's neuropharmacological properties, and studies with patients are complicated by clinical heterogeneity within a given DSM (Diagnostic and Statistical Manual of Mental Disorders) category. Thus, a drug that might be effective in a well-defined subgroup of patients with a specific DSM diagnosis may actually be abandoned due to a lack of effect in a larger group of patients. These challenges significantly increase the likelihood of failure when developing CNS drugs for treating psychiatric disorders compared to other fields.

How can neuro-pharmacology help?

CHDR uses a rational approach to drug development by studying well-characterised, drug-sensitive CNS functions. This approach provides better continuity with preclinical research, which is based on a mechanistic approach. Using NeuroCart®, CHDR can determine whether a test compound passes the blood-brain barrier and reaches the intended target in healthy subjects. Using pharmacological challenges relevant to psychiatric disease (see below), we can demonstrate in healthy subjects that the compound will likely affect specific systems. In patient studies, this approach allows us to identify the patients in which the compound will have the highest likelihood of exerting a therapeutic effect. Together with the sponsor, CHDR can even design the study to include subsets of patients with specific DSM diagnoses.



The pharmacological challenge: demonstrating effect in healthy subjects

The early stages in clinical drug development provide a unique opportunity to collect a wealth of pharmacological information. This information can then be used to optimise the next stages in development, or it can send the compound back to the drawing board.

To study the compound's effect as early as possible, CHDR developed a series of pharmacological challenges that can be used to demonstrate pharmacological effect in healthy volunteers. For example, in the field of psychiatry, the tetrahydrocannabinol (THC) challenge and the carbon dioxide challenge can be used to demonstrate the effects of antipsychotic and anxiolytic drugs, respectively. In addition, the scopolamine challenge and the mecamylamine challenge can be used to demonstrate the effects of drugs designed to improve cognitive functioning via muscarinic and nicotinic receptors, respectively.

Taking care of patients

Using the information obtained in early-phase clinical studies, researchers can design patient studies that are both safe and clinically relevant. CHDR has performed many trials in patient cohorts with a wide range of psychiatric disorders, and patient care always has the highest priority. Thus, when recruiting patients and obtaining informed consent, CHDR complies with the highest standards of medical ethics. Before, during, and after each study, the patients' safety and well-being are ensured by informing the patient's general practitioner and the attending psychiatrist regarding the details of the study.

Measuring outcomes and Trial@Home

Bridging preclinical perspectives – which focus on receptor pharmacology – with clinical perspectives – which focus on symptoms and outcome – is always an important goal. That's why CHDR developed an inclusive, comprehensive approach. To determine whether a test compound is effective and ready for a large clinical trial, we combine measuring CNS functions with more 'traditional' instruments such as the Positive and Negative Symptom Scale (PANSS) and the Montgomery-Åsberg Depression Rating Scale (MADRS).

Because measuring psychiatric parameters in a clinical research unit can be influenced by non-specific effects related to studying patients in this setting, CHDR developed several tools for measuring physiological and psychological parameters in patients from the comfort of their own home. This unique approach – which we call 'Trial@Home' – uses custom-designed smartphone apps in combination with portable devices such as the Vital Connect Health Patch® to monitor psychiatric symptoms and collect physiological data while the patient goes about his/her daily activities. Collecting these data in a more natural setting helps researchers better understand the test compound's effects.

Ready-for-Research

CHDR has also developed an innovative approach to recruiting patients. With Ready-for-Research, we can recruit and pre-screen patients who are interested in participating in future studies, and we can establish their baseline CNS functions using NeuroCart®. This approach ensures that when a specific study is ready to begin, CHDR already has a suitable patient cohort on hand. Using both functional and 'wet' biomarkers, we can also quantify systems that are relevant to the specific disease (for example, by measuring the hypothalamus-pituitary-adrenal axis and pro-inflammatory cytokines in connection with clinical depression). Essentially, before a clinical study is even ready, we've already performed an observational trial in these patients.

Why choose CHDR?

The Centre for Human Drug Research specialises in early-phase clinical drug research. CHDR's overall mission is to improve the drug development process by collecting as much information as possible regarding the candidate drug in the early phases of development. This information helps sponsors make informed decisions regarding the course of clinical development for their product.

Why choose CHDR?

Research at CHDR covers a wide range of fields, including the central nervous system (CNS) and pain, the cardiovascular system, haemostasis, immunology, and dermatology. In addition, CHDR is at the forefront in developing novel biomarkers and methods for measuring drug-related effects in all of these research areas.

Pharmacology matters

Whether studying a new cognitive-enhancing drug, a next-generation painkiller, or a new monoclonal antibody designed to treat rheumatoid arthritis, the goal is to determine how the compound's effects correlate with both the dose and blood concentration at any given moment. In addition, understanding which biological systems are activated is an essential first step towards quantifying this relationship. At CHDR, our focus on pharmacology is reflected clearly in what we call question-based drug development.

Question-based drug development

CHDR actively uses question-based drug development - or QBD - as a more rational approach to drug development compared to conventional approaches. QBD can be best described as a series of questions that are addressed throughout the process. These questions often seem simple enough, but failing to answer even one question - or even addressing the questions in the wrong order - can have dire consequences. Thus, using this approach can potentially save companies millions of dollars by helping predict a catastrophic issue early in the development process, before the more expensive latter stages (for example, large-scale clinical trials or the marketing phase).

From a general perspective, the most important questions are:

1. Does the biologically active compound and/or active metabolite(s) reach the intended site of action?
2. Does the compound cause its intended pharmacological and/or functional effect(s)?
3. Does the compound cause any unintended pharmacological and/or functional effect(s)?
4. Does the compound have a beneficial effect on the disease and/or clinical pathophysiology?
5. What is the compound's therapeutic window?
6. How does any variability with respect to the drug response in the target population affect the product's development?

Contact

To learn about CHDR's full range of services, contact us today.

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