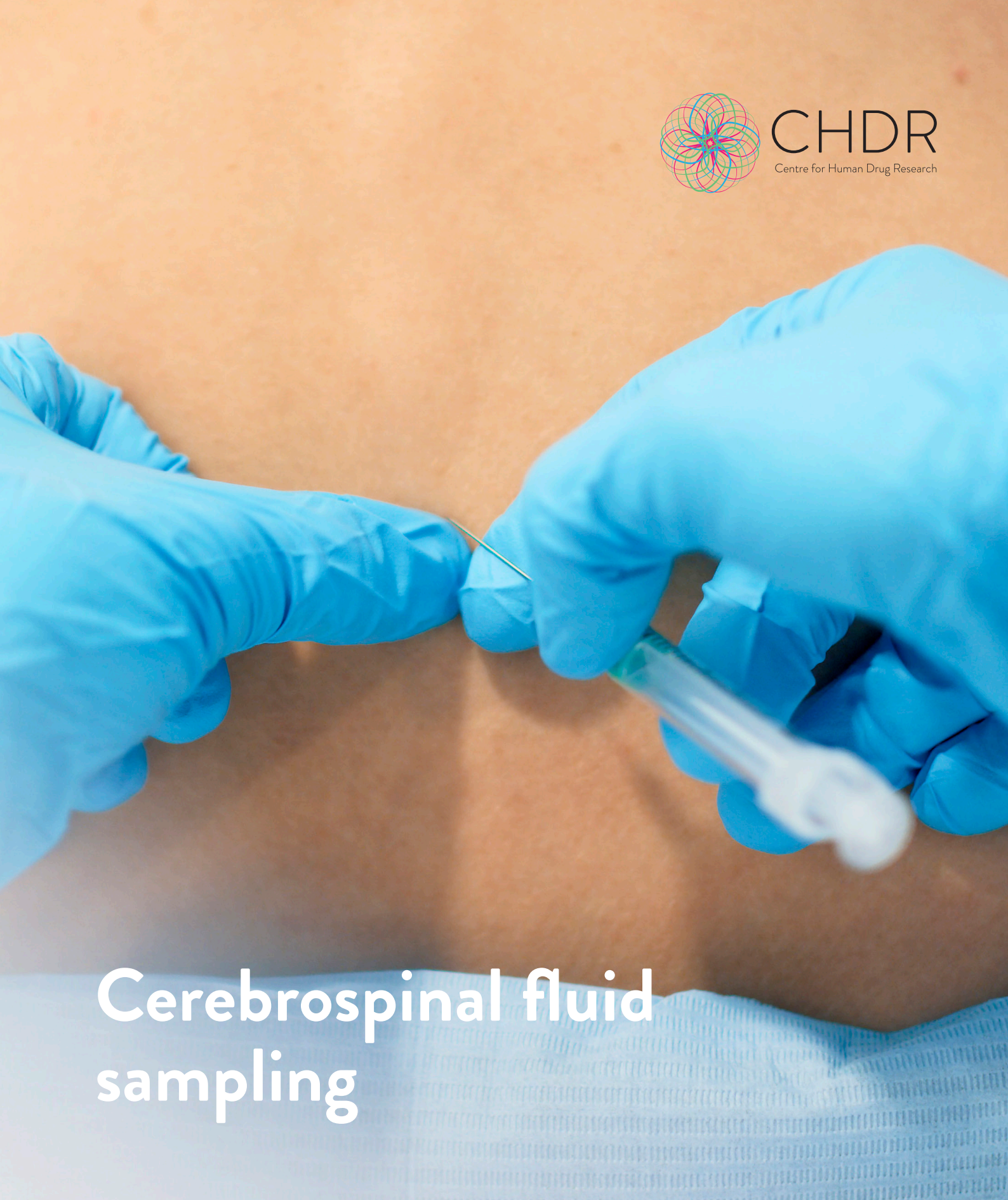


CHDR
Centre for Human Drug Research

Cerebrospinal fluid sampling

What CHDR offers:

- Extensive experience in early-phase clinical trials involving healthy volunteers and patients with a variety of conditions, especially neurodegenerative diseases
- Capacity to conduct numerous lumbar punctures (~300 single punctures per year) in our Clinical Research Unit
- Excellent quality of CSF collection with high success rate and less than 2% post-puncture headache
- An experienced and highly-trained team of physicians and two in-house neurologists assisted by dedicated nursing staff
- Expertise and support from the department of anaesthesiology of our partner hospital, the Leiden University Medical Center
- 24/7 pharmacy and bioanalytical laboratory facilities

Cerebrospinal fluid sampling

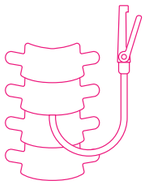
Sampling of cerebrospinal fluid (CSF) is an essential step for early-phase drug development studies, and particularly for studies in neurology. As CSF drug concentrations reflect unbound drug concentrations in the brain, this procedure is of critical importance for gaining insight into the delivery of drugs that act on targets in the central nervous system (CNS). In addition, CSF biomarkers are vital for indicating pharmacodynamic action of CNS drugs in clinical trials, as well as providing an excellent basis for go/no go decisions in the drug development process.

At CHDR we have an extensive track record in obtaining CSF samples in early-phase clinical trials, in healthy volunteers as well as patients with a variety of neurodegenerative diseases. Our close collaborations with academic and healthcare partners enable us to draw on the expertise of specialists from a range of fields, who play an active role in scientific discussions concerning study design and biomarker selection.

Cerebrospinal fluid sampling techniques applied at CHDR

Single lumbar puncture

- Performed under local anaesthesia
- Used for direct pharmacokinetic and/or pharmacodynamic assessments in the CNS compartment, as well as for intrathecal drug administration

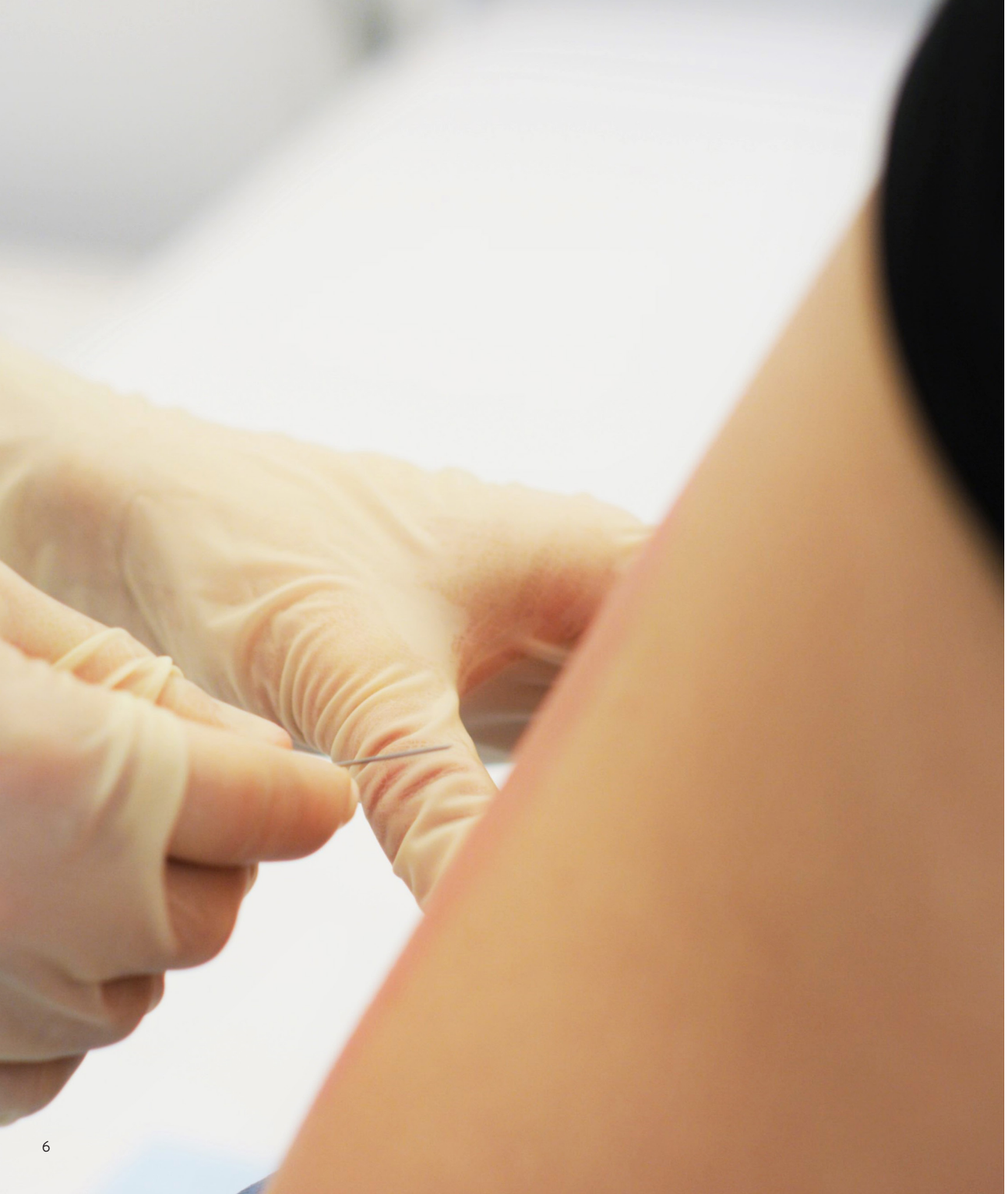


Continuous sampling with spinal catheter

- Performed under local anaesthesia
- Used when serial CSF sampling is needed for pharmacokinetic and/or pharmacodynamic profiling

Technical specifications

We use the Pencan® 25G spinal needle (B Braun, Germany) for single lumbar punctures and the Vygon spinal catheter set with 22G catheter with XRO line and catheter guide, open tip and 19G Tuohy needle (Vygon Nederland B.V.) for indwelling CSF taps. Specific choices of materials and equipment can be tailored according to study requirements.



Highlights of recent projects involving CSF sampling include:

- efficiently identifying healthy elderly with Alzheimer's disease pathology for participation in clinical trials. 200 lumbar punctures were performed in one year in healthy elderly individuals with normal cognitive functioning.

200 lumbar punctures
Healthy elderly

- identifying pharmacokinetic and pharmacodynamic effects of anti-tau antibody treatment in healthy elderly and patients with Alzheimer's disease (phase 1). 156 lumbar punctures (4-5 per subject) were performed over a period of twenty months.

156 Lumbar punctures
Healthy elderly
Alzheimer's disease patients

- measuring concentrations of an investigational drug and its potential effects on markers of neuronal degeneration in the brains of amyotrophic lateral sclerosis (ALS) patients (phase 1). 40 lumbar punctures were performed in 10 ALS patients receiving the potential new treatment.

40 Lumbar punctures
ALS patients

- investigating the neurogenerative process in Parkinson's disease by vaccinating healthy volunteers with a compound activating the subject's own immune system (and targeting alpha-S) (phase 1). 100 lumbar punctures were performed in healthy volunteers (mainly elderly).

100 Lumbar punctures
Healthy volunteers (mainly elderly)

- measuring brain concentrations of a potential new drug for Parkinson's disease and assessing the drug's potential to inhibit an overactive protein that may be involved in causing the disease (phase 1). Around 40 lumbar punctures were performed in 36 healthy volunteers.

40 Lumbar punctures
Healthy volunteers

- gaining insight into the pharmacokinetic and pharmacodynamic characteristics of an intrathecally administered compound (once through spinal catheter, second through single lumbar puncture) against Huntington's disease (phase 3).

Spinal catheter administration
Single lumbar puncture administration

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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