CHDR
Centre for Human Drug Research

Trial@home

non-invasive home-based assessment of drug effects in early clinical psychiatric drug development

Various novel drugs and innovative treatment approaches are currently being developed to treat mood, anxiety and trauma-related disorders. These new therapeutic options call for a methodological paradigm shift in early clinical central nervous system (CNS) drug development. There is a need for reliable instruments to quantify the effect of drugs in health and disease, not only under direct supervision in a clinical research unit, but also in the home environment. The Centre for Human Drug Research (CHDR) has developed and validated the Trial@home platform for this purpose.

Summary

- An innovative therapeutic paradigm for the treatment of mood, anxiety and trauma-related disorders is currently emerging in psychiatry.
- Novel compounds with mechanisms of action that are fundamentally different from conventional drugs are currently in development.
- These compounds tend to alter consciousness transiently, and following its resolution, therapeutic effects start to emerge within hours (eg. rapid acting).
- In contrast to conventional drugs, therapeutic effects are sustained for days or weeks after elimination following single or limited number of administration(s).
- Since both in-clinic and home-based assessments of efficacy and safety in real time are needed to reliably capture these dynamics, incidental rater-based assessments using retrospective interviews are inadequate.
- CHDR developed Trial@home, which is an innovative, integrated remote monitoring platform to collect both objective behavioural and safety data and self-reports while study participants go about their daily lives.
- The platform is built around the needs of clinical trials and embodies 'privacy by design' to ensure data privacy.
- Trial@home has been successfully deployed in more than 15 clinical trials and has been validated for the estimation of symptom severity in patients with major depressive disorder (MDD) in the home environment.

After decades in which few truly new drugs have reached patients, psychiatric drug discovery and development is currently undergoing a revival. New treatments are being developed that offer hope to patients worldwide in whom existing treatments are only marginally effective or ineffective.

From the perspective of clinical drug development and trial design, these new treatments present various challenges. In particular, a limited number of drug administrations may already demonstrate sustained effects, meaning that such compounds no longer require chronic dosing and subjects cannot be monitored over time in the clinical unit. In addition, some of the novel therapeutic approaches involve the combination of a (single) dose of a compound and intensive psychotherapy.

Truly informative clinical trials that study such novel treatments call for reliable tools that assess both acute and sustained drug effects prospectively in real time. This requires measurements to take place not only within the clinic, but also in the study participant's home environment. CHDR's Trial@home remote monitoring platform provides the infrastructure and tools needed to achieve this.

A new therapeutic paradigm in psychiatry

The current pharmacological treatment of mood, anxiety and trauma-related disorders largely relies on the modulation of monoaminergic neurotransmitter systems. With such compounds, therapeutic effects typically become evident after several weeks of treatment. However, novel agents are now being developed that act via recently-reidentified targets, such as the serotonergic 5-HT_{2A} receptor, or engage new targets altogether, such as the glutamatergic NMDA receptor. These compounds tend to induce acute effects that may transiently alter the state of consciousness, therapeutic effects occur rapidly (within hours to days) after acute consciousness-altering effects have dissipated, and therapeutic effects are sustained long after the compound has been eliminated. Examples include drugs such as (es) ketamine, dimethyltryptamine (DMT), psilocybin, 3,4-Methylenedioxymethamphetamine (MDMA) and a number of investigational medicinal products currently in early development.

Although transient consciousness-altering effects occur in healthy volunteers and patients alike, the sustained (therapeutic) effects are typically not expected to occur in healthy volunteers. This means that proof-of-concept studies should be designed to include characterisation of sustained drug effects in selected patient populations over time. Such measurements therefore must also be able to take place outside the research unit.

The need for real-time, real-world measurements

A new therapeutic paradigm in psychiatry also requires a novel approach to measuring drug effects. The classical approach is based on rater-based assessments using instruments such as the Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Åsberg Depression Rating Scale (MADRS). In this approach, the clinician conducts interviews in which patients are required to report on their mood and activity levels retrospectively. However, the use of such measurements in clinical trials is associated with methodological drawbacks. When administered by researchers, the interview itself may have unintended therapeutic effects. Moreover, these interviews tend to show larger therapeutic effects in research settings/research units compared to naturalistic environments. This leads to overestimation of the drug's therapeutic potential and decisions could be taken based on skewed information. For these reasons, both efficacy and safety outcomes based on retrospective, subjective reports are not suitable for most novel compounds currently under development.

To characterize the efficacy and safety of these compounds optimally, behavioural assessments that objectively measure daily fluctuations in symptom severity over longer periods of time as patients go about their everyday lives should be integrated in clinical trials. Several remote digital technologies that can be deployed prospectively are currently available, paving the way for reliable, home-based measurements to be integrated seamlessly in a range of clinical trials. Non-invasive, automated implementation of minimally invasive, objective behavioural measures and subjective measures of patient experience has the potential to revolutionise early drug development in psychiatry, not only by addressing current methodological concerns related to outcome measures, but also by limiting the burden on study participants and reducing overall trial costs.

Trial@home: a versatile and widely applicable platform for remote monitoring in clinical trials

Trial@home, developed by CHDR, is a fully equipped remote monitoring platform that leverages digital technology to collect data from patients or healthy volunteers as they go about their daily lives. Designed from the ground up to facilitate clinical studies, Trial@home has already been used in more than 15 trials involving more than 500 study participants. The versatile, cloud-based platform can be deployed in various ways depending on the compound under study, the research question, and specific client requirements. The data collected can serve as primary measures or can be used to complement measurements taken in our Clinical Research Unit. The collected data also have the potential to assess safety related parameters (e.g., blood pressure, body temperature, etc.).

The communication hub of the Trial@home platform is the participant's mobile phone, which serves as the gateway for data collection. Behavioural data may be collected from sensors in the phone itself, as well as via connected devices such as smartwatches or blood pressure monitors. These measurements provide a detailed objective picture of the study participant's level of physical activity and social interactions.

Digital technologies are integrated in the platform only after thorough validation has taken place (see box Trial@home validation). The range of validated measures is constantly being expanded, and currently includes (also see picture below):

- Sleep patterns and sleep quality
- Blood pressure
- Weight
- Body composition
- Body Temperature
- Spirometry
- Steps / activity / mobility
- Geolocation
- Sound / voice analysis
- Social / interpersonal interactions*
- Smartphone usage

In addition to objective behavioural measurements, an electronic patient-reported outcome (ePRO) system is integrated in the Trial@home platform, which enables quantification of the subjective experience of study participants. The client's choice of questionnaire can be delivered at pre defined moments in the trial, whereby participants can report on their anxiety, stress and depression using validated, state-of-the-art scales. Participants can also be asked to submit media such as photos as part of their interaction with the platform.

* Trial@home detects when study participants engage in conversations using the phone's built-in microphone, but for privacy reasons the actual conversations are not recorded.

Validating Trial@home for the estimation of depression severity

Innovation is at the core of CHDR's approach to early clinical drug development. In validating new technologies for use in clinical trials, such as the Trial@home platform, we follow standardised procedures for technical, analytical, and fit-for-purpose validation.

As part of an ongoing process to ultimately validate the platform for use in antidepressant drug trials, CHDR performed an investigator-initiated study in which prospective observational data was collected from a representative population of outpatients with depression, as well as age- and sex-matched healthy controls. A machine learning model was developed that distinguished healthy volunteers from patients, on the basis of a granular assessment of subjective affective states combined with data on smartphone interaction and social and physical activity. In addition, depression symptom severity could be estimated with 80% accuracy using a combination of geolocation and smartwatch measurements.

The model development process begun with the full list of possible measurements, from which a subselection was made based on their importance for the research question and the degree of burden on participants. This resulted in a reduced set of measurements that were not only able to quantify depression symptom severity but also easy to acquire, minimising the effort required from the study participants. This is illustrated in the figure below.

Trial@home validation

Validation steps for using Trial@home to study drug effects in major depressive disorder (MDD)

- ✓ Technical validation of digital devices
- ✓ Model to distinguish between healthy volunteers and MDD patients based on Trial@home measurements
- ✓ Model to estimate MDD severity based on Trial@home measurements
- → Demonstrate sensitivity of MDD severity model to a rapidly acting antidepressant drug

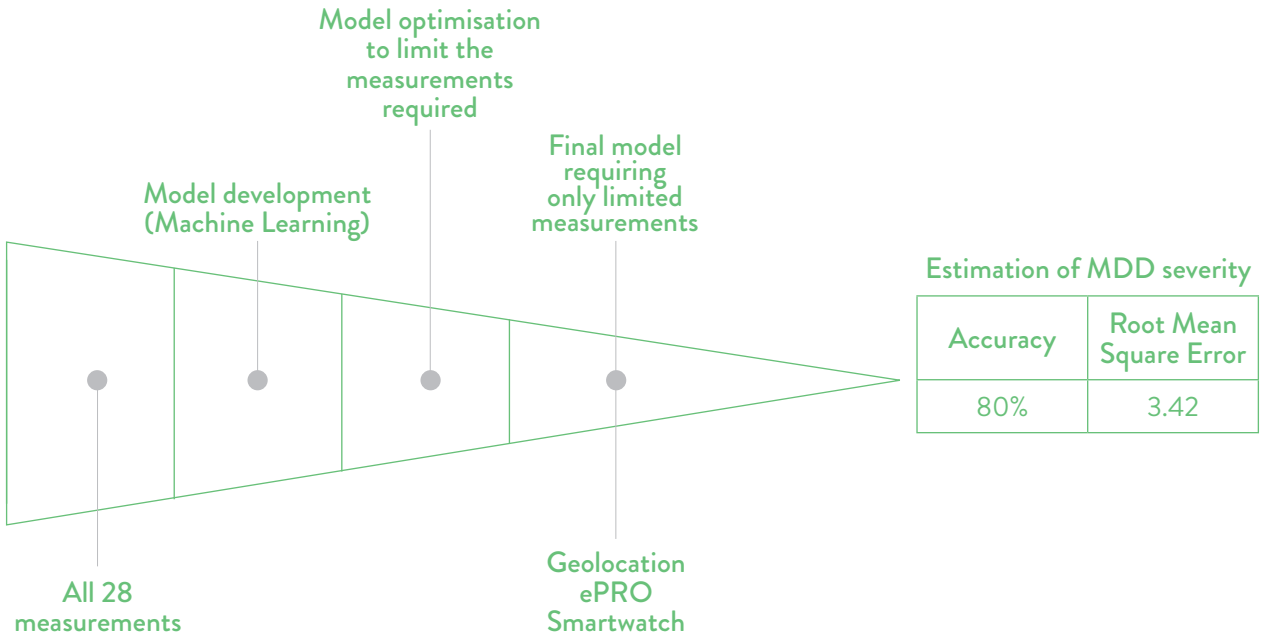

Figure: Process of developing the model for MDD severity estimation. Starting from the full set of measurements leading to a minimised easy to measure set with 80% accuracy in MDD severity estimation.

Assessment of antidepressant (AD) drug effects using Trial@home

Following the first validation studies, the next step should demonstrate the potential of the Trial@home platform to capture efficacy following administration of a novel, rapidly acting AD with sustained effects in a relevant patient group. CHDR is currently preparing a proof-of-concept study with single-dose ketamine as "rapidly-acting reference AD" in major depressive disorder (MDD). Ketamine, a non-competitive NMDA receptor antagonist, is well characterised in terms of AD effects and safety using the classical approach of retrospective reporting. In this trial, Trial@home will be validated as a way to monitor sustained AD effects following the principles presented in this White Paper. If this study is successful in demonstrating sensitivity to the antidepressant effects of ketamine, CHDR plans to offer Trial@home in future sponsored trials involving novel, potentially rapidly acting antidepressants in MDD. The use of Trial@home in this trial is visualised in the following figure.

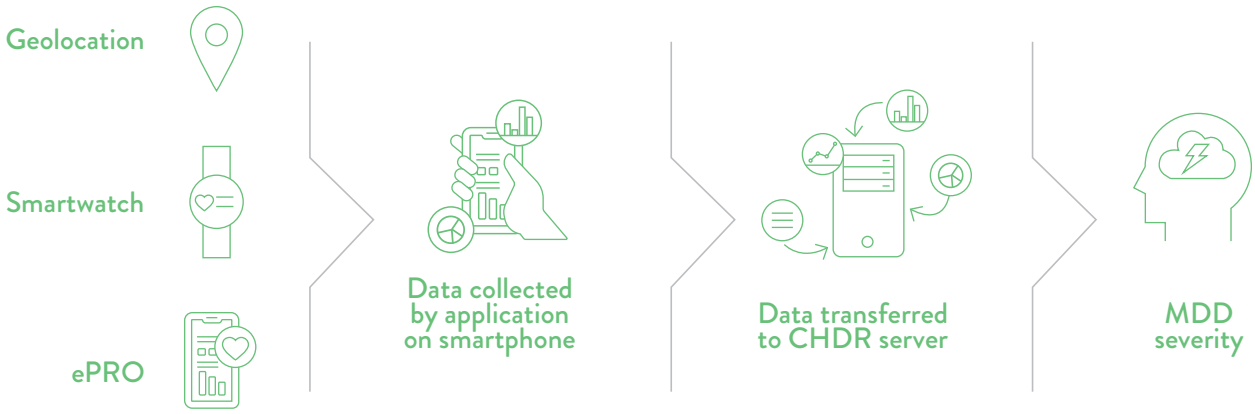

Figure: Measurements and MDD severity estimation in a rapidly acting antidepressant drug trial.

Privacy by design

CHDR has designed and developed the Trial@home platform from the ground up to facilitate the needs of clinical trials. As a clinical research organisation where participants' privacy is a central concern, we applied the principle of 'privacy by design', taking compliance with the relevant regulations as our starting point. The Trial@home platform complies with the GDPR of the European Union and assures that participant data is safe, secure and reliable in every step of the process.

The privacy of study participants' data is ensured at every stage of the data lifecycle. We employ the highest technical standards in encryption and security, and contract market leaders to provide these services. Alongside this, our thorough standard operating procedures form a robust framework that minimises the scope for human error. Trial@home has been successfully used in more than 15 clinical trials so far, involving both patients and healthy volunteers.

Besides privacy, the safety and dignity of participants is always paramount in our study designs. Performing measurements in the daily life of participants could potentially be considered intrusive. Therefore, we only ever measure what is needed to achieve the goals of the study, and the reason why a specific measurement is performed is always explained in detail to study participants. Trial designs that incorporate Trial@home are routinely accepted by the Netherlands' medical ethics committee, which acknowledges the platform's added value for clinical drug research.

Want to know more?

We hope this brief overview gives you an idea of the possibilities of the Trial@home platform, powered by CHDR's extensive experience in early clinical drug development. We enjoy providing a tailored service to meet our clients' needs and hope to contribute to the development of novel treatments in psychiatry and other fields in coming years. Responses to this paper and inquiries about Trial@home are welcome at info@chdr.nl.

List of publications

1. Zhuparris, A., Maleki, G., Koopmans, I., Doll, R., Voet, N., Kraaij, W., Cohen, A., van Brummelen, E., De Maeyer, J., Groeneveld, G. (2023). Smartphone and Wearable Sensors for the Estimation of Facioscapulohumeral Muscular Dystrophy Disease Severity: Cross-sectional Study. *JMIR Form Res*, 7:e41178. https://formative.jmir.org/2023/1/e41178 DOI: 10.2196/41178
2. Van Diemen, M. P. J., Ziagkos, D., Kruizinga, M. D., Benard, M. R., Lambrechtse, P., Jansen, B. A. M., Gademan, M. G. J., Cohen, A. F., Nelissen, R. G. H. H., Groeneveld, G. J. (2022). Mitochondrial function, grip strength, and activity are related to recovery of mobility after a total knee arthroplasty. *Clinical and Translational Science,* 00:1-12. https://doi.org/10.1111/cts.13441
3. Maleki, G., Zhuparris, A., Koopmans, I., Doll, R.-J., Voet, N., Postma, O., Cohen, A., van Brummelen, E., Groeneveld, G. J., De Meyer, J. (2022). Objective Monitoring of Facioscapulohumeral Dystrophy During Clinical Trials Using a Smartphone App and Wearables: Observational Study. *JMIR Formative Research,* https://formative.jmir.org/2022/6/e31775/
4. Stuijt, D. G., Exadaktylos, V., Bins, A. D., Bosch, J. J., van Oijen, M. G. H. (2022). Potential rola of smartphone-based passive sensing in remote monitoring of patients with cancer. *JCO Clinical Cancer Informatics,* 6:e2200079. https://doi.org/10.1200/CCI.22.00079
5. Kruizinga, M. D., Zhuparris, A., Dessing, E., Krol, F. J., Sprij, A. J., Doll, R.-J., Stuurman, F. E., Exadaktylos, V., Driessen, G. J. A., & Cohen, A. F. (2022). Development and technical validation of a smartphone based pediatric cough detection algorithm. *Pediatric Pulmonology*, 57, 761-767. https://doi.org/10.1002/ppul.25801
6. Elzinga, W., Prins, S., Borghans, L., Gal, P., Vargas, G., Groeneveld, G., Doll, R. (2021). Detection of Clenbuterol-Induced Changes in Heart Rate Using At-Home Recorded Smartwatch Data: Randomized Controlled Trial. *JMIR Form Res,* 5(12):e31890, https://formative.jmir.org/2021/12/e31890 DOI: 10.2196/31890.
7. Sverdlov O., Curcic J., Hannesdottir K., Gou L., De Luca V., Ambrosetti F., Zhang B., Praestgaard J., Vallejo V., Dolman A., Gomez-Mancilla B., Biliouris K., Deurinck M., Cormack F., Anderson J.J., Bott N.T., Peremen Z., Issachar G., Laufer O., Joachim D., Jagesar R.R., Jongs N., Kas M.J., Zhuparris A., Zuiker R., Recourt K., Zuilhof Z., Cha J.H., Jacobs G.E. (2021). A Study of Novel Exploratory Tools, Digital Technologies, and Central Nervous System Biomarkers to Characterize Unipolar Depression. *Front Psychiatry,* 6;12:640741. https://doi.org/10.3389/fpsyt.2021.640741
8. Kruizinga, M. D., Moll, A., Zhuparris, A., Ziagkos, D., Stuurman, F. E., Nuijsink, M., Cohen, A. F., & Driessen, G. J. A. (2021). Postdischarge Recovery after Acute Pediatric Lung Disease Can Be Quantified with Digital Biomarkers. *Respiration.* https://doi.org/10.1159/000516328
9. Zhuparris, A., Kruizinga, M. D., Gent, M. Van, Dessing, E., Exadaktylos, V., Doll, R.-J., Stuurman, F. E., Driessen, G. A. & Cohen, A. F. (2021). Development and Technical Validation of a Smartphone-Based Cry Detection Algorithm. *Frontiers in Pediatrics,* 9, 262. https://doi.org/10.3389/fped.2021.651356
10. Lambrechtse, P., Ziesenitz, V. C., Atkinson, A., Bos, E. J., Welzel, T., Gilgen, Y., Gürtler, N., Heuscher, S., Cohen, A. F., & van den Anker, J. N. (2021). Monitoring the recovery time of children after tonsillectomy using commercial activity trackers. *European Journal of Pediatrics,* 180(2), 527–533. https://doi.org/10.1007/s00431-020-03900-4
11. Kruizinga, M. D., Stuurman, F. E., Exadaktylos, V., Doll, R. J., Stephenson, D. T., Groeneveld, G. J., Driessen, G. J. A., & Cohen, A. F. (2020). Development of novel, value-based, digital endpoints for clinical trials: A structured approach toward fit-for-purpose validation. *Pharmacological Reviews,* 72(4), 899–909. https://doi.org/10.1124/pharmrev.120.000028
12. Kruizinga, M. D., Essers, E., Stuurman, F. E., Zhuparris, A., van Eik, N., Janssens, H. M., Groothuis, I., Sprij, A. J., Nuijsink, M., Cohen, A. F., & Driessen, G. J. A. (2020). Technical validity and usability of a novel smartphone-connected spirometry device for pediatric patients with asthma and cystic fibrosis. *Pediatric Pulmonology,* 55(9), 2463–2470. https://doi.org/10.1002/ppul.24932
13. van Brummelen, E. M. J., Ziagkos, D., de Boon, W. M. I., Hart, E. P., Doll, R. J., Huttunen, T., Kolehmainen, P., & Groeneveld, G. J. (2020). Quantification of tremor using consumer product accelerometry is feasible in patients with essential tremor and Parkinson's disease: a comparative study. *Journal of Clinical Movement Disorders,* 7(1). https://doi.org/10.1186/s40734-020-00086-7
14. Rijsbergen, M., Rijneveld, R., Todd, M., Feiss, G. L., Kouwenhoven, S. T. P., Quint, K. D., van Alewijk, D. C. J. G., de Koning, M. N. C., Klaassen, E. S., Burggraaf, J., Rissmann, R., & van Poelgeest, M. I. E. (2020). Results of phase 2 trials exploring the safety and efficacy of omiganan in patients with human papillomavirus-induced genital lesions. *British Journal of Clinical Pharmacology,* 86(11), 2133–2143. https://doi.org/10.1111/bcp.14181
15. Kruizinga, M. D., Zuiker, R. G. J. A., Sali, E., de Kam, M. L., Doll, R. J., Groeneveld, G. J., Santen, G. W. E., & Cohen, A. F. (2020). Finding Suitable Clinical Endpoints for a Potential Treatment of a Rare Genetic Disease: the Case of ARID1B. *Neurotherapeutics,* 17(3), 1300–1310. https://doi.org/10.1007/s13311-020-00868-9
16. Rijsbergen, M., Niemeyer-van der Kolk, T., Rijneveld, R., Pinckaers, J. H. F. M., Meshcheriakov, I., Bouwes Bavinck, J. N., van Doorn, M. B. A., Hogendoorn, G., Feiss, G., Cohen, A. F., Burggraaf, J., van Poelgeest, M. I. E., & Rissmann, R. (2020). Mobile e-diary application facilitates the monitoring of patient-reported outcomes and a high treatment adherence for clinical trials in dermatology. *Journal of the European Academy of Dermatology and Venereology,* 34(3), 633–639. https://doi.org/10.1111/jdv.15872
17. Kruizinga, M. D., Stuurman, F. E., Groeneveld, G. J., & Cohen, A. F. (2019). The future of clinical trial design: The transition from hard endpoints to value-based endpoints. In *Handbook of Experimental Pharmacology* (Vol. 260, pp. 371–397). Springer. https://doi.org/10.1007/164_2019_302