CRA PORTFOLIO — DOOR 3

ADULT ADHD DIGITAL BIOMARKER FEASIBILITY ASSESSMENT

Phase II Site Feasibility Assessment

Digital Biomarker-Aided ADHD Diagnostic Protocol

Charité Universitätsmedizin Berlin | Vivantes Netzwerk für Gesundheit

> *"The signal is present.*
>
> *The instrument to receive it has not been built."*

Martha

May 2026

Contents

01 — The Problem This Study Is Addressing

The signal is present. The instrument to receive it has not been built.

There is no validated digital endpoint for adult ADHD in Europe. The European Medicines Agency qualification framework exists. The qualified biomarker does not. What exists instead is a diagnostic infrastructure calibrated to performance: to the clinical presentation of inattention, impulsivity, and dysregulation in the room where assessment happens. That infrastructure has a structural blind spot, and the population most consistently falling through it is not the most severely affected. It is the most adapted.

This feasibility study proposes to begin building the instrument specifically for a population whose diagnostic invisibility is structural rather than incidental: adult women with suspected or unrecognised ADHD, with West African heritage, resident in Berlin. The study uses actigraphy, continuous performance testing, and smartphone passive monitoring across a seven-day window. The feasibility question it addresses is whether passive digital monitoring can produce data of sufficient reliability and participant retention to support a future pivotal validation trial in this population.

That is what this document proposes. What it is certain about, and what it is genuinely still finding out, are both named here.

02 — Why the Measurement Problem Is Real

Adult ADHD in high-functioning populations, and in West African immigrant women specifically, does not present to assessment the way assessment was designed to receive it. Three distinct mechanisms produce the same composed clinical surface. Current diagnostic tools distinguish between none of them.

Mechanism One — Physiological Adaptation

A neurodivergent person managing chronic sensory and cognitive load over years develops a shifted baseline. The accumulation is real and the recalibration is real: what registers as severe impairment in a body without that history registers differently in one that has been running the load for decades. The pain tolerance literature documents a parallel mechanism in Black women: self-reported severity scores systematically revised downward by clinicians, biological difference invoked where acquired adaptation is the accurate explanation. The same attribution error operates in attention assessment. The scale was not calibrated on this body.

Mechanism Two — Conditioned Suppression

In many West African households, and across the diaspora they produced, visible expression of difficulty was not available as a behaviour. Composure was survival. By the time a woman shaped by this enters a diagnostic room, the hold is not a strategic choice. It is how the nervous system operates. The assessment receives a performance it cannot read as data.

Mechanism Three — Absent Infrastructure

Women from healthcare systems where access was contingent on payment, where self-advocacy was not the operating assumption, where you did not perform for a right you were never taught you had, arrive in European clinical settings without the grammar of entitlement. The assessment reads the silence as absence of symptom. The silence is the absence of a tool that was never in the kit.

> **Three different mechanisms. One clinical surface. One interpretation. Wrong three ways simultaneously.**

Passive digital monitoring addresses all three for the same reason: it does not require the performance the clinical room expects. Actigraphy, continuous performance testing, and smartphone interaction data are collected in the environment where the masking load is actually running, not the appointment during which it is temporarily suspended.

A woman managing full cognitive masking across a working week, filtering communication output, regulating sensory environment, sustaining social performance within tolerable limits, is not resting between appointments. By day three the physical cost is already running: disrupted sleep, accumulated muscular tension, elevated baseline fatigue, progressive depletion of the reserves that make the surface possible. She continues.

> **The somehow she continues is the data. Passive monitoring measures it.**

03 — Why Berlin. Why These Sites. Why Now.

Berlin is the right location for this study because the population is here and the infrastructure to recognise it is not.

The city has a significant and growing West African immigrant community. It has two major medical centres with documented ADHD diagnostic capacity and documented demand exceeding that capacity. It has a healthcare system that is, in specific pockets, developing the reflex to recognise neurodivergence in non-standard presentations, and in others has not yet begun.

The United Kingdom provides the comparator. In several UK cities, a West African immigrant woman presenting to primary care and disclosing an ADHD or autism diagnosis will be met with a recognition response that is imperfect, uneven, inconsistent across settings, but present. The reflex exists. In Berlin, the equivalent presentation is more likely to be met with a response that precedes language: a response that communicates, before a single clinical question has been asked, that this presentation is not the expected one. The UK developed the recognition reflex, imperfectly, ahead of Germany. Berlin has the population. It does not yet have the reflex. That gap is the reason to do the study here.

Site Selection Rationale

Charité Universitätsmedizin Berlin is the proposed primary research site. The rationale is operational: documented infrastructure for ADHD assessment, academic research capacity, and a closed waitlist that constitutes direct evidence of unmet diagnostic demand. Charité is proposed not because it is perfect but because it has the structural capacity to run this study and documented proof that the population it would serve is already attempting to access it.

The closed waitlist is not a recruitment obstacle. It is the recruitment argument. A study offering diagnostic access as a participation incentive to patients who cannot access standard care occupies the exact position a feasibility study should occupy: it addresses an unmet need while generating the data that would make a larger trial possible.

Vivantes Netzwerk für Gesundheit provides the comparative frame. It is not a proposed research site. It is embedded institutional knowledge of what inadequate diagnostic infrastructure looks like in practice. Side-by-side comparison of the two institutions sharpens the feasibility framework: what makes Charité viable is legible precisely because what makes Vivantes unsuitable is documented. A site feasibility framework that cannot articulate the difference between a functional and a non-functional site is not a feasibility framework. It is a preference.

04 — The Proposed Biomarker Battery

The battery is structured across three evidence tiers. Tier designations are explicit and honest. No signal is presented at a higher evidence level than the literature supports.

Tier One — Established: Actigraphy and Rest-Activity Rhythm

Protocol: Seven-day continuous wrist actigraphy. Outcome variables: interdaily stability (IS), intradaily variability (IV), L5 onset timing, relative amplitude, and sleep efficiency.

Walter et al. (BMC Psychiatry, 2026) provide the primary adult evidence base: 54 adults with ADHD monitored over 10 days against 47 controls showed significantly lower IS in the ADHD group (M = 0.450 versus M = 0.488, p = 0.029, moderate effect size), with delayed L5 onset consistent with circadian phase shift as a feature of adult ADHD rather than a secondary symptom of sleep disturbance. Tonetti et al. (Journal of Psychiatric Research, 2018) identified absence of a post-lunch dip in motor activity as a potential trait marker of adult ADHD, a circadian signal distinct from sleep disruption alone. Boonstra et al. (Sleep, 2007) established the seven-day monitoring window as a sufficient interval for baseline rest-activity characterisation in adult ADHD populations.

The adult evidence base remains thin relative to the paediatric literature. That gap is this study's primary scientific justification: the signal exists and is measurable in adults, but adult-specific validation is precisely what is absent.

Evidence level: Established signal, adult validation emerging. | Tier: Primary.

Tier Two — Validated: Continuous Performance Testing

Protocol: Single 20-minute CPT session at baseline, administered in-site. Outcome variables: omission errors (inattention), commission errors (impulsivity), reaction time variability.

Edebol et al. (PsyCh Journal, 2013) report sensitivity of 86% and specificity of 83% for a composite QbTest+ measure when comparing ADHD patients to healthy controls. Independent peer-reviewed review confirms this figure does not hold against clinical patient comparators: specificity fell to 41% when the comparator was patients with bipolar II disorder rather than normative controls (Lohr et al., Frontiers in Psychiatry, 2020). The clinical utility of QbTest+ therefore lies in supporting comprehensive assessment rather than replacing it.

Charité's ADHS-Spezialsprechstunde explicitly lists neuropsychological procedures including continuous performance testing as part of its diagnostic methodology. This study is not introducing a foreign instrument. It is augmenting an existing diagnostic pathway with digital biomarker validation.

Evidence level: Validated, existing infrastructure at proposed site, limitations documented. | Tier: Primary.

Tier Three — Novel: Smartphone Passive Monitoring

Protocol: Seven-day passive monitoring via RADAR-base platform or equivalent. Outcome variables: notification response latency (questionnaire and social/communication applications), ambient light variability, active session duration.

Sankesara et al. (JMIR Formative Research, 2025) provide the foundational prospective observational evidence: 20 adults and adolescents with ADHD monitored alongside 20 controls over 10 weeks showed five of ten digital signals with significant group differences and moderate-to-high effect sizes (d = 0.64 to 1.13). Notification response latency and ambient light variability were among the strongest signals. The study explicitly calls for larger future studies to assess whether these markers can track ADHD severity or predict outcomes. This feasibility study sits in exactly that pipeline position.

The seven-day window proposed here is shorter than the ART study's 10-week window. This is a deliberate feasibility decision: participant burden is a documented retention risk in this population, and the shorter window tests whether meaningful signal can be obtained within a practically sustainable timeframe.

Evidence level: Prospective observational, pilot stage, large effect sizes, explicit call for replication. | Tier: Exploratory.

Battery Summary

Instrument	Protocol	Evidence Level	Tier	Key Limitation
Wrist actigraphy	7-day continuous wear	Established, adult gap	Primary	Adult validation thin vs paediatric literature
Continuous Performance Test	Single 20-min baseline session	Validated, infrastructure exists	Primary	Discriminative validity vs clinical populations imperfect
Smartphone passive monitoring	7-day RADAR-base passive	Prospective observational, pilot	Exploratory	Single prior study; short window may reduce signal

05 — Site Profile

Comparative Analysis: Charité and Vivantes

Element	Charité Universitätsmedizin Berlin	Vivantes Netzwerk für Gesundheit
ADHD diagnostic service	ADHS-Spezialsprechstunde, documented and active	Public documentation confirms general psychiatric outpatient capacity only; no specialist ADHD infrastructure identified in public sources. Embedded institutional knowledge from clinical practice at Vivantes Hospital Berlin confirms this assessment.
Current demand status	Closed to new registrations, very large demand (December 2025)	Not applicable; no specialist ADHD capacity documented
CPT infrastructure	CPT confirmed in diagnostic methodology; neuropsychologische Verfahren listed explicitly	Not identified in public documentation
Academic research capacity	Full university hospital: ethics committee, research coordinators, IMP management	Non-academic hospital network; limited research infrastructure
Ethics committee	Charité Ethikkommission: approximately 8 weeks to Votum	Separate process; longer estimated timeline
Referral pathway	Facharztüberweisung required; Berlin/Brandenburg catchment	General psychiatric referral; no specialist overflow pathway
Site designation	PRIMARY RESEARCH SITE	COMPARATIVE REFERENCE. Not proposed as research site.

06 — Risk Matrix and Mitigation Strategy

Category	Specific Risk	Probability	Impact	Mitigation Strategy
Recruitment	Population access through closed primary site	Medium	High	Partnership with Charité overflow referral; patient organisation engagement; GP network outreach in West African community organisations
Retention	Study burden given masking load cost in this population	Medium-High	High	Seven-day window deliberately short; passive monitoring minimises active participation; participant compensation; flexible scheduling
Regulatory	EU MDR Class IIa Notified Body requirement for composite battery	High	Medium	Pre-submission regulatory consultation before protocol finalisation; Notified Body engagement at protocol stage; instrument tiering separates diagnostic from exploratory

Data governance	GDPR Article 9 high-risk processing of special category health data	High	High	DPIA mandatory prior to recruitment; privacy-by-design; pseudonymisation at source; local data processing; granular consent with partial withdrawal option
Biomarker	Signal-to-noise ratio in novel tier insufficient for feasibility threshold	Medium	Medium	ART study prior data (d=0.64–1.13) informs power estimate; novel tier pre-specified as exploratory; success threshold defined a priori
Site capacity	Charité waitlist limits active patient flow	Medium	High	Vivantes PIA as secondary referral source pending capacity-building; community organisation partnerships as non-clinical recruitment channel
Composite performance	Unknown interaction between three instrument modalities	Unknown	High	Pre-specified signal hierarchy with primary and exploratory designations; three modalities reduce single-point failure risk

07 — Regulatory and Data Governance Framework

EU MDR Classification

The composite biomarker battery, as a software-informed clinical decision support tool, falls under EU MDR 2017/745 Software as a Medical Device (SaMD) classification. Under Rule 11, software intended to inform diagnosis of a serious condition is classified at minimum as Class IIa, requiring Notified Body review. The battery cannot be self-certified.

Instrument tiering addresses this operationally. QbTest+ as an established CPT with existing CE marking presents a lower regulatory burden. The actigraphy component, used for monitoring rather than standalone diagnosis, may qualify for a lower classification under intended use specifications. The smartphone passive monitoring component is designated as a research-only data collection platform in this feasibility phase, deferring its regulatory classification pathway to the pivotal trial stage when the evidence base justifies it.

> *Regulatory anchor: EU MDR 2017/745, Annex VIII Rule 11. EMA Qualification of Novel Methodologies guidance, EMA/CHMP/SAWP/72894/2008.*

GDPR and Data Protection

Continuous behavioural monitoring of neurodivergent adults constitutes high-risk processing of special category health data under GDPR Article 9 and the German DSGVO equivalent. A Data Protection Impact Assessment is mandatory before any recruitment commences. The privacy architecture is a design condition, not a compliance addendum.

A community that has historically had its data collected without its direct benefit will not participate in a study that does not demonstrate, operationally, that its privacy is a design priority. The consent architecture therefore includes: explicit, granular, informed consent in the participant's strongest language; the right to withdraw individual data streams without withdrawing from the study entirely; clear data retention and destruction timelines; and a plain-language privacy notice that does not assume familiarity with European data protection frameworks.

> *Regulatory anchor: GDPR Article 9; DSGVO §22; ICH E6(R2) §4.8 informed consent; §5.1 quality assurance; §5.18 monitoring requirements.*

08 — What This Study Proposes to Demonstrate

This study is built on certainty about the problem and structural confidence in the design. The uncertainty it names is genuine and methodologically honest.

What Is Certain

The population exists in Berlin, is not being diagnosed at the rate its presence warrants, and is currently absorbing the cost of that non-recognition in ways that are measurable and are not being measured. The three mechanisms described above are the lived operational architecture of the women this study is designed to reach. A diagnostic instrument that requires clinical

performance will continue to miss them. A passive instrument that follows the body across its actual week will not.

What Is Structurally Confident

Actigraphy and smartphone passive monitoring have established feasibility signals in ADHD populations in other contexts. The EMA qualification pathway is open. The site has the infrastructure. The population has the need and the proximity. The GDPR Article 9 privacy-by-design architecture addresses the data sensitivity of a health study in an already-marginalised community, not as a compliance obligation but as a condition of legitimate research in this context.

What Is Genuinely Open

Whether seven-day passive monitoring produces data of sufficient signal-to-noise ratio in this specific population to meet the reliability threshold required for a future pivotal trial. Whether participant retention across the monitoring window is achievable given the masking load that makes daily life expensive and additional study burden a real variable. Whether the composite biomarker performs better than any single modality alone, and by how much.

These are the feasibility questions. They are open because this study has not been done. Claiming otherwise would not be science. It would be the same attribution error this study is designed to correct.

> **The aim is not to prove what we already know. It is to build the instrument that makes what we know measurable, reliably enough that a regulator can trust the measurement, and specifically enough that the population it was built for is no longer invisible inside it.**

09 — Forward Signal

This feasibility assessment is the front end of a larger protocol concept currently in development. The Phase II feasibility questions addressed here, specifically site viability, retention rates, and signal quality across three instrument tiers, generate the data required to power a future pivotal validation trial. That protocol exists as a working document and will be made available to the right institutional partner at the appropriate stage of engagement.

A systematic review of adult ADHD digital biomarker validation in European populations does not currently exist in peer-reviewed literature. The scoping review embedded in this feasibility assessment maps the existing evidence base and identifies the gaps that a formal systematic review would address. That publication is a planned output of the research trajectory this document initiates.

10 — References

Biomarker Battery — Tier One: Actigraphy

Walter A, Martz É, Weiner L, et al. Sleep, rest-activity rhythm, cognitive and emotional symptoms in adult ADHD: unraveling the links with an actimetry-based approach. *BMC Psychiatry.* 2026;26:317. https://doi.org/10.1186/s12888-026-07947-9

Biomarker Battery — Tier One: Circadian Trait Marker

Tonetti L, Conca A, Giupponi G, Filardi M, Natale V. Circadian activity rhythm in adult attention-deficit hyperactivity disorder. *Journal of Psychiatric Research.* 2018;102:254–260. https://www.sciencedirect.com/science/article/abs/pii/S0022395618301286

Biomarker Battery — Tier One: Adult Actigraphy Baseline

Boonstra AM, Kooij JJS, Oosterlaan J, Sergeant JA, Buitelaar JK, Van Someren EJW. Hyperactive night and day? Actigraphy studies in adult ADHD: a baseline comparison and the effect of methylphenidate. *Sleep.* 2007;30(4):433–442. https://doi.org/10.1093/sleep/30.4.433

Biomarker Battery — Tier Two: QbTest+ Validation

Edebol H, Helldin L, Norlander T. Measuring adult attention deficit hyperactivity disorder using the Quantified Behavior Test Plus. *PsyCh Journal.* 2013;2(3):48–58. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3832237/

Biomarker Battery — Tier Two: QbTest+ Clinical Review

Lohr D, Weidler M, Bartels M, Falck-Ytter T, Konrad K. The quantified behavioral test as a confirmatory test in adult ADHD diagnosis: independent review of discriminative validity. *Frontiers in Psychiatry.* 2020;11:216. https://doi.org/10.3389/fpsyt.2020.00216

Biomarker Battery — Tier Three: Smartphone Passive Monitoring

Sankesara H, Denyer H, Sun S, Deng Q, Ranjan Y, Conde P, Rashid Z, Asherson P, Bilbow A, Groom MJ, Hollis C, Dobson RJB, Folarin A, Kuntsi J. Identifying digital markers of attention-deficit/hyperactivity disorder (ADHD) in a remote monitoring setting: prospective observational study. *JMIR Formative Research.* 2025;9:e54531. https://doi.org/10.2196/54531

Circadian Review

Coogan AN, McGowan NM. A systematic review of circadian function, chronotype and chronotherapy in attention deficit hyperactivity disorder. *Attention Deficit and Hyperactivity Disorders.* 2017;9(3):129–147. https://doi.org/10.1007/s12402-016-0214-5

Regulatory — EU MDR

EU Regulation 2017/745 on medical devices (EU MDR). Official Journal of the European Union, 5 April 2017. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32017R0745

Regulatory — EMA Biomarker Qualification

European Medicines Agency. Qualification of novel methodologies for drug development: guidance to applicants. EMA/CHMP/SAWP/72894/2008. https://www.ema.europa.eu/en/qualification-novel-methodologies-drug-development

Regulatory — ICH E6(R2)

ICH E6(R2). Good Clinical Practice: Integrated Addendum. International Council for Harmonisation, 2016. https://www.ich.org/page/efficacy-guidelines

Regulatory — ICH E9(R1)

ICH E9(R1). Addendum on Estimands and Sensitivity Analysis in Clinical Trials. International Council for Harmonisation, 2019. https://www.ich.org/page/efficacy-guidelines

Regulatory — GDPR Article 9

Regulation (EU) 2016/679 (General Data Protection Regulation), Article 9. Special categories of personal data. https://gdpr-info.eu/art-9-gdpr/