technopolis group

Understanding decision-making and barriers in the Mental Health R&D ecosystem

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Final report

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Acronyms

ABPI	Association of the British Pharmaceutical Industry
ACT-EU	Accelerating Clinical Trials in the EU
AI	Artificial Intelligence
AMARI	African Mental Health Research Initiative
AMP	Accelerating Medicines Partnership
BC	Biomarkers Consortium
BeCOME	Biological Classification of Mental Disorders
BfArM	Federal Institute for Drugs and Medical Devices
BMBF	Federal Ministry of Education and Research
BMG	Federal Ministry of Health
BRC	Biomedical Research Centres
C-I-R-C	Centre for Intervention and Research on Adaptive and Maladaptive Brain Circuits
CBT	Cognitive Behavioural Therapy
CEMHRI	Centre for Mental Health Research and Initiative
CHR	Clinical High-Risk
CRN	Clinical Research Network
CTIS	Clinical Trials Information Systems
CTTI	Clinical Trial Transformation Initiative
DBS	Deep Brain Stimulation
DiGA	Digital Health Applications
DSM	Diagnostic and Statistical Manual of Mental Disorders
EC	European Commission
EEG	Electroencephalogram
EMA	European Medicines Agency
EVAs	Early Valuation Assessments
FAST	Fast-Fail Trials
FDA	Food and Drug Administration

FNIH	Foundation for the National Institutes of Health
GMHPN	Global Mental Health Peer Network
HIC	High-Income Country
HPA	Hypothalamic-Pituitary-Adrenal
HTA	Health Technology Assessment
IAPT	Increasing Access to Psychological Therapies
ICD	International Classification of Diseases
ICER	Institute for Clinical and Economic Review
ICF	Informed Consent Form
IMDRF	International Medical Device Forum
IMI	Innovative Medicines Initiative
IPG	Implantable Pulse Generator
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; Institute for Quality and Efficiency in Healthcare
IVDR	In Vitro Diagnostic Medical Device Regulation
LMIC	Low and Middle-Income Country
LoA	Likelihood of Approval
MAT	Minimally Adequate Treatment
MDD	Major Depressive Disorder
MDR	Medical Device Regulation
MH-TRC	Mental Health Translational Research Collaboration
MHM	Mental Health Mission
MHRA	Medicines and Healthcare products Regulatory Agency
MHRGs	Mental Health Research Groups
MoA	Mechanism of Action
MRC	Medical Research Council
NGO	Non-Governmental Organisation
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research

PoS	Probability of Success
PRU	Policy Research Unit
PWLE	People With Lived Experience
R&D	Research and Development
RCT	Randomised controlled trial
RDN	Research Delivery Network
REC	Research Ethics Committee
ROI	Return on Investment
SAFMH	South African Federation for Mental Health
SAHPRA	South African Health Products Regulatory Authority
SaMD	Software as Medical Device
SCZ	AMP Schizophrenia
TRD	Treatment-Resistant Depression
UKRI	UK Research and Innovation
UnitedGMH	United for Global Mental Health
VR	Virtual Reality
WEF	World Economic Forum
WHO	World Health Organization

Executive Summary

Mental health challenges affect the daily life of millions of people worldwide. Yet current treatments may not be available for many or provide only limited effectiveness for certain mental health conditions. This reality underscores the urgency for further research and investment into understanding these conditions better and developing new and better interventions.

Wellcome has commissioned Technopolis to undertake a study to understand the decision-making processes of developers of mental health interventions and identify barriers, their root causes and possible solutions within the mental health R&D ecosystem. The study explored the mental health R&D landscape in four country contexts (i.e. in the US, the UK, Germany, and South Africa) and focused on three mental health conditions: anxiety, depression, and psychosis. The scope of intervention types included pharmaceuticals, medical devices, and digital therapeutics.

The study followed a mixed-method research approach, drawing on data from a variety of sources: literature review, interviews, case studies, workshops, and a compilation of quantitative data. It included a set of analytical packages:

1. Development of a typology of mental health interventions
2. Characterisation of the mental health R&D ecosystem, including market sizes, pipelines and R&D pathways of different mental health interventions along the innovation life cycle to approval/accreditation and early uptake
3. Analysis of key stages in the decision-making process of developers of mental health interventions
4. Identification and prioritisation of the longlist of documented barriers and potential solutions through dedicated workshops
5. Development of recommendations for research funders and investors to foster and promote the development of innovative, inclusive and equitable interventions.

The stakeholder consultation covered over 100 individuals from a broad range of stakeholder groups: developers, regulators and policymakers, investors and funders, advocacy groups, people with lived experience, and healthcare providers. The study was guided by a bespoke expert advisory group[1], with a range of expertise, including lived experience, clinical, regulatory, R&D and innovation.

1 Membership of the Expert Advisory Group: Steve Appleton, Professor James Barlow, Professor Hugo Critchley, Hayden Holmes, Dr Thomas Kabir, Dr Nicholas Prior, Claudia Sartor, Dr Farhad Shokraneh, Dr Divya Srivastava, and Professor Karin Waldherr.

Characterisation of the mental health R&D ecosystem

The mental health R&D ecosystem is complex, with various key stakeholders, often specific to the type of intervention, and spans a series of defined stages from proof-of-concept or prototype of an intervention to regulatory approval, followed by market launch and uptake. While pharmaceutical R&D follows a well-established pathway, medical devices and digital therapeutics (i.e. software as a medical device) may follow a markedly different route. These require a risk-based classification to determine whether the intervention needs further testing in clinical trials. For medical devices, self-certification or conformity assessment is needed before these can be placed on the market. Digital therapeutics pose particular challenges both for developers and regulators due to rapid technological progress, and pathways vary substantially across jurisdictions.

Developer decision-making

Seven case studies were developed that exemplify developers' decision-making processes in identifying the unmet need, proposed solution, engaging with stakeholders and routes to market. The case studies include:

- gameChange, a digital intervention that leverages virtual reality to address agoraphobia-related avoidance and discomfort in people with psychosis.
- deprexis®, a web-based digital therapeutic platform offering self-help programmes for managing unipolar depression and depressive disorders. Evidence of effectiveness was generated through several randomised controlled trials.
- Woebot, an automated conversational agent (chatbot) on a smartphone specifically targeting adults, adolescents and mothers with stress, anxiety, and depression.
- Digital Pill by Inner Cosmos, an implantable medical device using transcranial magnetic stimulation for the treatment of depression.
- OAK by Fisher Wallace Labs, a wearable medical device for Cranial Electrotherapy Stimulation for the treatment of depression and other neuropsychiatric and cognitive disorders.
- Boehringer Ingelheim combine a 'transdiagnostic' approach and precision psychiatry (including pharmaceuticals and complementary digital therapeutics) for a range of mental health conditions including the treatment of symptoms relating to major depressive disorder, post-traumatic stress disorder, schizophrenia, and borderline personality disorder.
- Psychedelics-based treatment for mental health conditions, which explores the historical background and challenges in research and development of this class of pharmaceuticals with specific examples.

Involvement of People with Lived Experience

Involvement of people with lived experience was identified as an essential element of the mental health R&D process, from research and product design, through participant recruitment to accelerating translation of research results into policies and healthcare practices. This co-production between developers and people with lived experience contributes to ensuring the relevance and acceptability of mental health R&D and helps the eventual adoption and uptake of the intervention. Engaging with people with mental health conditions for developers is however often challenging.

Similarly, the involvement of people with lived experience was crucial in the current research study. Consulting with them ensured their perspectives were reflected in the data collection tools, engagement strategy and the drafting of the report. Lived experience advisors felt that their involvement contributed to a collaborative and respectful environment that encouraged meaningful participation and input from all stakeholders. Study researchers felt that involving lived experience expertise and perspective significantly enhanced their understanding of perspectives and shaped their research approach, reinforcing their commitment to inclusivity and relevance in mental health research.

Priority barriers and current efforts to address these

This study developed a list of 12 scientific and 10 non-scientific barriers which were organised into a hierarchical typology with three top-level areas:

- High development costs
- Complex regulatory and policy environment
- Lack of attractiveness of the mental health market to developers, investors, and funders

High development costs were largely rooted in gaps in scientific knowledge and failure rates of mental health clinical trials, linked to the lack of biomarkers and animal models to robustly measure the effects of mental health interventions, clinical heterogeneity of mental health conditions, challenges in clinical trial recruitment and retention, and challenges in designing appropriate placebo for clinical trials. These ultimately lead to results that do not translate to real-world scenarios.

Developers, funders, and investors face significant challenges navigating the complex regulatory and policy environment for market access, which hinders product development and adoption. This is especially true for small companies developing innovative and digital therapeutics, who find the authorisation, pricing, and reimbursement models particularly difficult. Consequently, they often seek direct access to alternative well-being markets, frequently without sufficient evidence of effectiveness.

Developers and investors do not perceive the regulated mental health treatment market as attractive with sufficient return on investment for mental health interventions. This is due to demand-side challenges linked to low

treatment-seeking and/or low adherence to treatment by patients, and health professionals not prescribing adapted treatments for patients (further widening treatment gaps).

There are several current initiatives to help address some of the barriers identified in the mental health R&D ecosystem. We collected these initiatives and expanded further the list of potential solutions by exploring adjacent areas with relevance to specific barriers in mental health, for example:

- Pain where biomarkers are not available to support R&D
- HIV where stigma is stifling treatment-seeking behaviour
- Developing antimicrobial drugs where market failure/no return on investment is a significant challenge
- Rare diseases where low numbers of patients and the need for real-world evidence present bespoke challenges.

The specific initiatives are listed in the report and the accompanying appendices.

Recommendations for future actions

The R&D pathway that developers of mental health interventions need to navigate represents a 'leaky research pipeline', suffering from attrition at various stages. Research funders and investors with an interest in mental health therapeutics could focus on three main types of actions to leverage their influence:

- Funding to encourage and enable innovation through financial support for educational activities, research programmes, and infrastructure development to drive innovation and accessibility in mental health research.
- Convening to catalyse collaborations by bringing stakeholders together to launch campaigns, workshops, and regulatory discussions, fostering collaboration and best practice sharing.
- Advocating and influencing to drive change in the research funding landscape, policy and regulatory context of mental health interventions, and for the meaningful involvement of individuals with lived experience.

The mental health R&D pathway, from research to early adoption of solutions, has several key challenges identified and described in the study. We provide specific recommendations for future actions to address the challenges which the community identified as being the largest blockers to progress:

1. Gaps in basic scientific knowledge about the biological mechanisms of mental health conditions and the lack of suitable animal models make hypothesis-driven traditional experimentation challenging, especially for pharmaceuticals and medical devices. As a result, researchers and developers may therefore decide not to enter the technology development pathway to target mental health conditions. The following actions (in synergy) could unblock this barrier in the longer term:

- Fund large-scale interdisciplinary research programmes to attract talent to the field
- Convene global multi-stakeholder meetings to develop a strategic re-

search agenda

- Advocate for an increase in global research funding into mental health research to match the share of its disease burden
- Fund a mental health R&D funds tracking portal and monitor investment trends and priorities.

2. Challenging participant recruitment and retention in clinical studies further exacerbates clinical research in mental health. The root causes are stigma, fear and negative perceptions in a vulnerable participant cohort, among others, contributing to developers' perception of high risk of obtaining the required sample sizes. Research funders, investors and other stakeholders could consider the following actions:

- Fund research initiatives that develop linked datasets, tools and methods for better identification of subtypes of mental health conditions
- Fund the expansion of a global Lived Experience Network to create local champions that developers can engage with and who can support participant recruitment to trials
- Advocate for the importance of mental health research in the broader population through engagement with mental health charities and networks of PWLE
- Advocate for the use of enhanced informed consent forms in mental health trials that are clear, comprehensive, and culturally sensitive.

3. Trials results do not translate to real-world scenarios for various reasons, e.g. the efficacy of interventions under trial conditions not matching that of the home environment, the clinical heterogeneity of mental health conditions, and marginalised groups not being involved in clinical trials. Consequently, there can be multiple lines of action to ensure that future mental health interventions produce positive outcomes:

- Fund the development and use of innovative trial methodologies, including adaptive, pragmatic, and decentralised trials that collect real-world (digital) data as evidence for regulators
- Fund large-scale demonstrators to provide a platform for digital therapeutics developers to test, validate, and optimise emerging technologies and systems at scale
- Fund trials that ensure the inclusion of people historically underrepresented in mental health research to ensure equity of health outcomes of the interventions developed, e.g. through diversity-enhancement strategies in clinical trials
- Advocate for research led by people with lived experience to empower them, foster trust with developers, and ensure relevance of research
- Advocate for the involvement of peo-

ple with lived experience in the selection of outcome measures, ensuring they align with the experiences, priorities and perspectives of the target population.

4. Regulatory uncertainty related to obtaining marketing authorisation poses a significant challenge, especially for innovative approaches and digital therapeutics. The study has shown that regulatory science and practice are not always able to accept novel data and evidence generated by developers, and in some drug types, such as psychedelics, there are legal and regulatory hurdles to obtaining marketing authorisation. The following actions may be taken by research funders to help to address the issue:

- Convene international forums to foster collaboration and knowledge-sharing among regulators, aiming for more efficient and globally aligned regulatory frameworks on areas of relevance for mental health interventions
- Convene meetings focussed on controversial interventions, such as psychedelics, and facilitate discussions to address regulatory obstacles effectively
- Advocate for the recognition of mental health as a global unmet medical need and unblock regulatory incentives to accelerate marketing authorisation for mental health technologies.

5. The variability and complexity of pricing and reimbursement models across global markets pose significant challenges. Fragmented national rules around cost-effectiveness assessment and health system recommendations vary greatly, adversely affecting developers' decisions about the attractiveness of regulated markets. This makes scaling up products regionally a costly endeavour, especially for smaller developers of digital therapeutics. Research funders and investors may consider the following actions:

- Convene international forums to foster collaboration and knowledge-sharing among health technology assessment (HTA) bodies, aiming for more efficient and globally aligned scientific frameworks on areas of relevance for mental health interventions and specifically for digital therapeutics
- Advocate for the involvement of people with lived experience in decision-making on the most effective mental health products to ensure their perspectives are considered in assessments
- Fund clinical comparative effectiveness studies, specifically for small to medium-sized enterprises (SMEs), to develop evidence for submission to HTA and P&R bodies to facilitate entry of digital therapeutics to the regulated health market.

6. The alternative direct market access route for digital well-being products opens a new, faster and less costly route for developers of mental health products (often without sufficient evidence of effectiveness). The lack of evidence can create confusion for patients to choose the right product, the associated (out of pocket) cost may become a barrier to access for marginalised groups, and health professionals are unable to prescribe these well-being products. Research funders may use their power and influence to help tackle this problem by considering the following actions:

- Convene focus group discussions with industry on quality control measures and rigorous standards for mental health intervention development
- Fund a bespoke prize for developers of popular digital apps on the well-being market to demonstrate the effectiveness of their solutions and, on positive outcome, facilitate deployment and uptake of their product in the national health system
- Advocate for easier deployment and uptake of mental health interventions in the health systems.

7. Low treatment-seeking by patients driven by stigma, fear, or perception of not needing treatment, creates a significant 'treatment gap'. This gap represents demand-side challenges for developers, as the estimated large market size does not translate into real demand. This issue is particularly acute for marginalised groups and populations in LMICs. Moreover, this barrier is closely linked to the challenges of participant recruitment and retention in clinical studies, suggesting that similar actions may be considered to address both issues:

- Advocate for awareness programmes and information campaigns in target populations through engagement with mental health charities and networks of people with lived experience about the importance of recognising and seeking treatment for mental health conditions.

8. Access to patients is limited due to shortage of prescribing health professionals. The challenge of patients not presenting may be further exacerbated by health professionals not prescribing available treatments for patients. This leads to a lower apparent demand for new therapies by patients. Research funders may have limited options to unblock this barrier but could consider the following:

- Advocate for more education programmes for primary care providers about mental health and available treatment options
- Advocate for the integration of evidence-based digital interventions into healthcare delivery systems, highlighting their potential benefits in improving mental health outcomes.

1 Introduction

An increase in the research, development and use of safe and effective interventions in mental health is necessary to avoid mental health conditions becoming the leading burden of disease by 2030.[1]

Wellcome's vision for mental health is a world in which no one is held back by mental health problems. To advance this vision, Wellcome's mission over the next 20 years is to drive a step change in the ability to intervene as early as possible in the course of anxiety, depression, and psychosis, broadly defined, in ways that reflect the priorities and needs of those who experience them. As part of this vision, Wellcome has commissioned Technopolis to undertake a study to understand the decision-making and barriers in the mental health research and development (R&D) ecosystem from the perspective of the developers.

A vital aspect of Wellcome's mental health vision is finding new and improved interventions that remedy current treatment gaps, e.g. more effective treatments with fewer side effects that are more widely accessible to all sections of the public and available at lower cost.[2] However, existing barriers preventing or delaying the R&D of innovative solutions must be identified and addressed to encourage developers in the mental health field.

The progress of innovations along the pathway 'from bench to patient use' may encounter challenges at various stages, including scientific challenges (e.g. lack of understanding of biological processes underlying a condition), economic barriers (e.g. high development costs), and issues related to the wider ecosystem (e.g. the health system's ability to deliver solutions developed). The lack of inclusion of people with lived experience (PWLE) of mental health conditions (i.e. end users) in the development of mental health interventions poses a significant barrier to creating effective and inclusive solutions. Without their input, developers may struggle to understand the real needs of the target population, leading to interventions that are less relevant, acceptable, and impactful in addressing the unmet needs of mental health challenges.[3]

To foster and promote the development of effective interventions, it is necessary to identify existing barriers to progress, assess the extent to which this affects progress, and to understand their underlying root causes and interacting factors. The scope of the study is to collect data for three mental health conditions (i.e. anxiety, depression, and psychosis) that correspond to the focus of Wellcome's Mental Health Strategy from four different contexts (i.e. the US, the UK, Germany, and South Africa). Interventions in scope include pharmaceuticals, medical devices, and digital therapeutics.

The study undertaken by Technopolis aims to understand developers' decision-making processes and identify barriers and possible solutions within the mental health R&D

ecosystem, focusing on two overarching objectives:

1. **Develop greater understanding of the mental health R&D landscape:** By understanding and quantifying, where possible, the effects that both scientific and non-scientific challenges in the R&D ecosystem are having on the successful progression of mental health interventions from pipeline entry to initial uptake.
2. **Produce clear recommendations for research funders and investors to action:** To guide future decision-making and support prioritisation to address barriers within the R&D ecosystem, by identifying and exploring potential solutions.

This report draws together key data from a variety of sources (literature review, interviews, case studies, workshops and the compilation of quantitative data) to understand barriers and decision-making in the R&D ecosystem, highlighting the stakeholders' priority barriers with potential solutions in addressing these barriers. Firstly, by establishing a typology of mental health interventions, providing a framework for presenting the study's findings. This is followed by outlining the main features of the different R&D pathways, market sizes and pipelines for pharmaceuticals, medical devices, and digital therapeutics. Finally, the report highlights key barriers in the mental health R&D ecosystem and puts forward potential solutions and specific recommendations for research funders and investors.

2 Methodology

The study followed a comprehensive mixed-method research approach, using both qualitative and quantitative methods to gain a deep understanding of the mental health R&D ecosystem, key stakeholders' motivations and barriers in their decision-making processes for developing mental health interventions, and identify possible solutions for addressing universal barriers.

Table 1 presents an overview of the methodologies used for data collection and analysis to address the aims of the study. The detailed methodologies of data collection and the triangulation analysis are described in the following sub-sections.

Table 1 Overview of the methodologies used for data collection and analysis mapped to study aims

Aim	Analytical package(s)	Literature Review	Quantitative data compilation	Interviews	Case Study	Workshops
Understand the decision-making process that developers of mental health interventions follow across the mental health R&D ecosystem from development and funding, approval/accreditation, entry to market and initial uptake	• Characterisation of the ecosystem • Analysis of mental health intervention developers' decision-making	X	X	X		
Understand the critical points where the current ecosystem is not serving to support innovative and inclusive/equitable intervention development for mental health	• Characterisation of the ecosystem • Analysis of mental health intervention developers' decision-making	X		X	X	
Assess and where possible quantify the extent to which scientific and non-scientific challenges create barriers (e.g. gaps, blockages and hurdles) to the development through to approval and initial uptake of mental health interventions currently in the pipeline	• Prioritisation of universal barriers	X	X			X

Aim	Analytical package(s)	Literature Review	Quantitative data compilation	Interviews	Case Study	Workshops
Identify the push/pull factors that exist from regulators, policymakers, investors, end users & advocacy groups and other key stakeholders which influence the mental health R&D landscape throughout the lifecycle	• Identification of solutions	X		X	X	X
Assess how such hurdles can be overcome (or not) and/or identify what solutions are available to address these barriers	• Identification of solutions	X			X	X

2.1 Data collection

2.1.1 Desk research

2.1.1.1 Systematic literature reviews

As a first step to understanding and characterising the challenges in the mental health R&D ecosystem, we conducted a systematic literature review and targeted desk research to identify existing challenges and barriers. The barriers constitute a subset of challenges that prevent or delay the development and early adoption of mental health interventions in scope for the study, i.e. for pharmaceuticals, digital therapeutics, and medical devices.

A systematic literature review search strategy was designed to identify publications exemplifying key barriers (scientific and non-scientific). Articles for the review were sourced from bibliographic databases: Embase; MEDLINE; and PsycINFO. In addition, we also searched websites of organisations relevant in the mental health R&D ecosystem to identify relevant grey literature (see Appendix A). Keywords for the search were based on input from the project advisory group. The search strings are presented in Appendix A.

The literature search of bibliographic databases identified 2257 peer-reviewed articles that were screened for eligibility after removing 2205 duplicates. The search of grey literature sources identified 60 articles. All articles were initially screened for their potential relevance based on the title and abstract using the Rayyan software. 233 peer-reviewed articles and 20 grey literature articles were retained, sourced, and further screened for relevant content on challenges that prevent or delay the development and early adoption of mental health interventions. Ultimately, this process resulted in 13 relevant

articles. The majority of the articles screened did not contain relevant information on challenges, or were out of scope.

To expand the number of articles found using the systematic literature review, we conducted targeted desk research using separate searches for each mental health intervention type in scope (pharmaceuticals, digital therapeutics, and medical devices).

Publications were retained based on the relevance of the title and abstract and full texts were reviewed and relevant content on challenges was extracted. In addition, we also checked citations related to extracted content for additional information. An analysis of extracted content was performed to categorise key challenge themes which informed additional search terms to use for further rapid targeted desk research.

This process of iterative searches was continued until saturation was achieved and no new challenge themes emerged, or new articles were found, which resulted in an additional 78 articles being identified. A flow diagram for articles that were identified using search terms and strategy can be found in Appendix A. Data extracted from publications was synthesised against the key challenge themes that were identified as preventing or delaying the development and early adoption of mental health interventions.

This exercise resulted in a list of 12 scientific and 10 non-scientific barriers which were reviewed by the study's expert advisors. After in-depth discussions, the list of barriers evolved into a systematic typology over four levels, as shown in Appendix C. At the top level, barriers were categorised into three areas: (i) high development costs; (ii) complex regulatory and policy environment; and (iii) lack of attractiveness of the mental health market to developers, investors, and funders. The list of barriers was then presented to and prioritised by stakeholders during a workshop (see Section 1.1.1.1). Subsequently, we revisited the resources gathered in the original literature review and conducted further desk research to identify potential solutions related to these barriers in the mental health R&D ecosystem. To expand the list of potential solutions to barriers in the mental health space, we explored adjacent areas with relevance to specific barriers in mental health: pain (where biomarkers are not available to support R&D), HIV (where stigma is stifling treatment-seeking behaviour), developing antimicrobial drugs (where market failure/no return on investment is apparent), and rare diseases (where low numbers of patients and the need for real-world evidence present bespoke challenges). For the full systematic literature reviews on barriers and solutions, please see Appendix B and Appendix D.

2.1.1.2 Quantitative data compilation

To quantify the scale of identified barriers, we combined data form various sources, including both proprietary datasets and published studies. Each element of the quantitative analysis is described in more detail below.

Pharmaceutical clinical trials: to understand the progression along the R&D pathway, the study team utilised

Citeline's Trialtrove dataset[b] which provides global clinical trials intelligence for pharmaceutical products (excluding paediatric clinical trials which are not recorded in Trialtrove). The dataset includes information on enrolment and patient populations, study timelines, outcomes, and geographic distribution of sites. This report includes the analysis of Trialtrove data from global clinical trials conducted for the treatment of mental health conditions between 2013 and 2023. Twelve different health indications were included in the database, which were categorised into three broader groups, as presented in Table 2. These categories reflect the conditions for which there is Trialtrove data rather than a comprehensive list of conditions in scope of the study or a complete list of conditions under ICD11. Three indications within the scope of the study were not included in the analysis because Trialtrove did not have the data. These indications include perinatal anxiety, persistent depressive disorder, and postpartum psychosis.

For the purposes of our analysis, the long list of indications was grouped into three separate categories according to the similarity of symptoms.

Determining the appropriate groupings for these conditions was challenging because they share some overlapping symptoms, whilst also having significant differences in nature, severity, and diagnostic criteria. For example, while bipolar disorder includes depressive episodes, it is differentiated from depression by the requirement of at least one manic or hypomanic episode for diagnosis.

According to ICD-11, *'A depressive disorder should not be diagnosed in individuals who have ever experienced a manic, mixed or hypomanic episode, which would indicate the presence of a bipolar disorder.'*[c] Additionally, more than half of patients diagnosed with Bipolar Disorder develop psychotic symptoms during their lifetime, which tend to be more frequent during manic than depressive states.[d] As such, the study team included both Bipolar Disorder and Schizophrenia in one group, while presenting depression separately. We have used consistent grouping across all figures, including data analysis based on Globaldata.

[b] Trialtrove dataset, https://www.citeline.com/en/products-services/clinical/trialtrove

[c] ICD-11, Definition of Depressive disorder, https://icd.who.int/browse/2024-01/mms/en#1563440232

[d] Chakrabarti S, Singh N. Psychotic symptoms in bipolar disorder and their impact on the illness: A systematic review. World J Psychiatry. 2022 Sep 19;12(9):1204-1232. doi: 10.5498/wjp.v12.i9.1204. PMID: 36186500; PMCID: PMC9521535. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9521535/#:~:text=Psychosis%20in%20bipolar%20disorder%20(BD,depression%5B3%2D5%5D.

Table 2 Trialtrove health indication groupings

Anxiety	Depression	Psychosis
Body dysmorphic disorder	Major depression	Bipolar disorder
Generalised anxiety disorder	Perinatal depression/ postpartum depression	Schizophrenia
Obsessive compulsive disorder	Seasonal affective disorder/ seasonal depression	
Panic disorder		
Post-traumatic disorder		
Social anxiety disorder		

Note: The conditions included in the table reflect the conditions for which there is data in Trialtrove rather than a comprehensive list of conditions in scope of the study or a complete list of indications under ICD 11.

The study team employed this dataset to present information on diverse indicators, encompassing the percentage of industry-funded trials, the percentage of trials that successfully met their enrolment target, and the proportion of trials that concluded prematurely, along with an exploration of the reasons behind such terminations.

In addition to Trialtrove data analysis, we also utilised intelligence from separate Citeline's Datamonitor Healthcare reports[e] for Depression, Bipolar Disorder, and Schizophrenia. To provide further insight and a base for comparison, the figures for the 'psychiatry' and 'all indications' categories were sourced from a separate published report[f] that follows the same methodology and datasets as the Datamonitor Healthcare reports produced for this study. The estimates for the group called 'All indications' include 15 conditions: haematology, urology, endocrine, autoimmune, allergy, respiratory, infectious disease, metabolic, gastroenterology, psychiatry, cardiovascular, neurology, ophthalmology, oncology, and a category called 'others'.

Datamonitor Healthcare reports include information on the Probability of Success, Likelihood of Approval, and development timelines per phase. These estimates are based on information from Citeline's Biomedtracker, a database that tracks clinical development and regulatory history of investigational drugs to assess their likelihood of approval by regulators. The database is updated with information from press releases, investor and medical meetings, and regular communications with companies conducting clinical trials. It

[e] Datamonitor Healthcare reports, https://www.citeline.com/en/products-services/commercialization/datamonitor-healthcare

[f] 'Clinical Development Success Rates and Contributing Factors 2011–2020' report, https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf

includes information on whether a drug has advanced or been suspended at the end of a phase, as well as the time spent at each phase for all successful transitions. More information on these indicators is presented below:

- **Probability of Success (PoS) rates:** A phase transition refers to the progression from one clinical phase to the next, such as moving from Phase I to Phase II development or undergoing suspension upon conclusion of Phase I. These phase transition success rates were determined by taking the number of drugs moving from one phase to the next and dividing it by the total number of drugs progressing to the next phase and those that were suspended. Biosimilars and generic manufacturers developing novel investigational drugs were included in the analysis, but generic products were excluded.
- **Likelihood of Approval (LoA):** The likelihood of Approval denotes the probability of reaching regulatory approval from a drug programme's current phase of development. The figures were calculated as the product of individual PoS rates leading to regulatory approval.
- **Development Timelines:** The analysis of development timelines measured the time spent at each phase for all successful transitions, excluding suspended programme timelines. The time estimates represent the period between public announcement of the initiation of appropriate stages and, therefore, may not be an entirely accurate representation of clinical trial timelines. Each clinical phase transition may include more than one clinical trial, some of which run in parallel and others sequentially. Additional delays in between clinical trial phases caused by the reporting of trial outcomes, business decisions/planning or other reasons, are not included in the analysis.
- **Average clinical trial costs:** Citeline data also included estimates of the average clinical trial costs per phase and indication. Trial phase specific costs were taken from Sertkaya *et al*. (2016), and back calculated to provide a per patient cost for all three phases.[4] The per patient costs were then multiplied by trial recruitment data from Trialtrove to provide trial specific costings for each relevant indication. Per trial and per site costs provided in Sertkaya *et al*. (2016) were added accordingly without adjustment or back calculation. The number of trials used to inform the analysis is presented in Appendix E.
- **Devices (digital and non-digital) clinical trials**: the study team used the GlobalData Clinical Trial Database[9] contains information on medical device clinical studies and trials that are conducted across the globe. The database covers all medical device trials which are intended for diagnosis, treatment

[9] GlobalData Clinical Trial database, https://www.globaldata.com/marketplace/medical/medical-devices-clinical-trials/

and management of particular diseases, conditions, and/or symptoms. The distinction between clinical trials for digital and non-digital devices for the purposes of this analysis was done based on the market taxonomy as defined in the dataset, which refers to the classification of a medical device according to its use and therapeutic/diagnostic field. For digital devices, this is labelled as 'Healthcare IT', while non-digital medical devices include every other market classification provided in the dataset.

The categorisation into the different types of indications (depression, anxiety, psychosis) was done based on the 'indication' of the trial, which itself is defined as the therapeutic/diagnostic criteria for enrolment of the participants in the trial. This allocation took a similar approach to the one described in Table 2. This allocation is not mutually exclusive, meaning that one device may be applicable to more than one indication.

Information on the phase of clinical trials for medical devices is not widely used and most of the trials in the dataset lack information on the trial phase. However, where phase information is available, these refer to one, or a combination, of the following: Phase 0, Phase I, Phase II, Phase III, and Phase IV. To simplify this and ensure consistency with the analysis of pharmaceutical trials, in the presentation of our analysis, Phase I include all trials reported to be in Phase 0 and Phase I; Phase II trials include all trials reported to be in Phase I/II and Phase II; Phase III trials include all trials reported to be in Phase II/III, Phase III, Phase III/IV and Phase IV.

We rely on the reported trial status of each trial in the dataset, which is categorised as one of the following: planned, ongoing, completed, terminated, or withdrawn. Again, we adapt these categories to remain consistent with the analysis for pharmaceutical trials. The computation on the duration of trials is based on the reported start date and end date for each trial. We use information on the site location to compute the number (and status) of clinical trials being carried out in our countries of interest.

Marketed drugs: We used GlobalData's marketed drugs database to estimate the number of drugs with distinct mechanisms of action that are currently available on the market.[h] The database covers an extensive number of therapy areas and indications across 23 countries (see Table 3). For the purposes of our analysis, we extracted all available data for six separate regions (Global, Europe, US, UK, Germany, South Africa) and for the following mental health indications: anxiety disorders, depression, mania, psychosis, schizoaffective disorder, and schizophrenia.

[h] GlobalData Marketed and Pipeline Drugs database, https://www.globaldata.com/marketplace/pharmaceuticals/pipeline-marketed-drugs/

Table 3 Geographical scope of GlobalData marketed drugs database

North and South America	Europe	Asia and Oceania	Middle East and Africa
US, Canada, Mexico, Brazil	France, Germany, Italy, Spain, Austria, Belgium, Denmark, Switzerland, Russia, and United Kingdom	China, India, China, Indonesia, South Korea, Japan, Australia, New Zealand	Israel, South Africa

The products in scope include novel products, biosimilars, and generic product drugs. Data is gathered from regulatory authorities' websites, regulatory and financial registries, company websites, investor relations, public relations, and various other channels.

To estimate the number of drugs with distinct mechanisms of action, we de-duplicated the mechanisms of action column for each indication and country combination. We kept only the mechanism of action at the most advanced stage of development for each indication/country combination.

Pipeline drugs: We used GlobalData's pipeline drugs database to estimate the number of drugs with distinct mechanisms of action that are currently in the pipeline.[i] The database provides comprehensive profiles of pharmaceutical drugs at various stages of pre-clinical and clinical development, spanning from discovery to pre-registration. The dataset has a global coverage and the drugs in scope include novel human pharmaceutical drugs and biosimilars seeking market approval. Sources of information include drug announcements from developers published on company websites, and information on grants, publications, news, deals, conferences, regulatory and financial registries, and databases including clinicaltrials.gov. Our analysis of pipeline drugs with distinct mechanism of action covers the same indications and regions as the analysis of marketed drugs mentioned above.

Market size estimates: We used GlobalData's Drugs by Manufacturers database to estimate the total value of current and projected sales revenue generated by marketed and pipeline mental health drugs.[j] Equivalent data for digital and non-digital devices was not available. The dataset covers marketed innovator and biosimilar therapies approved by the EMA centralised pathway, UK MHRA, and/or the US FDA. The sales revenue information recorded in the dataset is sourced from company and prescription (Rx) drug sales, while the forecasts are derived from analyst consensus forecasts and patient-based forecasts derived from Disease

[i] GlobalData Marketed and Pipeline Drugs database, https://www.globaldata.com/marketplace/pharmaceuticals/pipeline-marketed-drugs/

[j] Globaldata: Drugs by Manufacturer Database, https://www.globaldata.com/marketplace/pharmaceuticals/drugs-by-manufacturer/

Analysis Report. The geographical scope of the dataset is the same as the one presented in Table 3. The data represents the total sales from all geographies where the company is marketing a given drug and cannot be disaggregated into specific regions or indications.

Marketed medical products: We used GlobalData's marketed medical devices database to estimate the number of digital and non-digital medical devices currently available on the market.[k] The dataset provides information on commercially available medical devices and diagnostic tests that have received approval since 2010. The data is primarily gathered from regulatory bodies around the world, as well as company websites, third-party press releases, conference presentations, investor presentations, and clinical trial registries. This database includes all medical devices that are used for diagnosing, managing, and treating mental health conditions, with the same groupings as presented in Appendix E. Digital therapeutics are defined as products with the following categories listed in the 'Market' column: Healthcare IT, Healthcare IT; Neurology Devices, Healthcare IT; Patient Monitoring Healthcare IT; Specialised Sectors, Healthcare IT; In Vitro Diagnostics. Medical devices (non-digital) include every other product in the dataset.

Pipeline medical products: We used GlobalData's pipeline medical devices database to estimate the number of digital and non-digital pipeline medical devices across different developmental stages, including 'early development', 'pre-clinical', 'clinical', and 'In approval process'.[l] The data is derived from secondary data sources, including company websites, grants, company reports, clinical trial registries, conference presentations, investor presentations, third-party news releases, among others. The dataset has a global geographical coverage. The split between digital and non-digital devices is the same as for marketed products (see above).

2.1.2 Stakeholder consultation

While desk research provides important insight into the current ecosystem, an in-depth qualitative exploration is needed to understand stakeholders' perspectives and real-world challenges specific to the development of mental health interventions. The stakeholder consultation consisted of a combination of interviews and workshops, with a diverse range of stakeholders identified through stakeholder mapping, see Table 4. Sampling for specific consultation activities aimed to ensure geographical coverage of stakeholders, types of interventions, and mental health conditions within the scope of the study.

[k] GlobalData: Marketed medical devices, https://www.globaldata.com/marketplace/medical/medical-device-marketed-products/

[l] GlobalData: Pipeline medical devices, https://www.globaldata.com/marketplace/medical/medical-device-pipeline-products/

Table 4 List of stakeholder groups consulted in the study

Stakeholder group	Description
Developers of mental health interventions (pharmaceutical and non-pharmaceutical)	Industry associations and representatives from a mix of large, established companies, SMEs and start-ups, digital app and MedTech companies, and academic developers.
Regulators and Notified bodies	Various regulators may be involved in the approval/marketing authorisation of pharmaceutical and non-pharmaceutical solutions. E.g. National Competent Authorities (medicines, medical devices, etc.) Health Technology Assessment bodies, Pricing and Reimbursement bodies, and Notified bodies.
Investors and funders	Private investors (VCs and seed funds) and international (public and third-sector) R&D funders active in mental health.
Policymakers	National and international policymakers are active in developing agendas relevant to mental health intervention developers from Departments/Ministries of Health, WHO Mental health unit.
Advocacy Groups	Civil society advocacy groups relevant to depression, anxiety, and psychosis.
People with lived experience	People with lived experience were identified and invited to participate via several lived experience networks developed or coordinated by expert advisors on our team.
End users	End users were interviewed in relation to case studies of specific interventions.
Primary, secondary and community health care providers	Institutional, community and family care providers were interviewed regarding their experience with early access barrier for mental health interventions.

2.1.2.1 Stakeholder interviews

A total of 57 semi-structured stakeholder interviews were conducted (Table 5). The interviews were designed to fill information gaps in the published literature, and identify additional challenges through topic guides adapted to specific stakeholder groups:

- Interviews with developers were designed to explore decision-making pathways, motivators of decision-making, and identifying challenges
- Interviews with regulators and policymakers were designed to understand the regulatory push/pull factors that are in place as well as gather their perspective on gaps and barriers in the regulatory system
- Interviews with investors and funders were designed to explore how funding decisions are made – prioritisation of where to invest and

how evidence for such decision-making is sourced and presented

- Interviews with healthcare providers were designed to explore their level of engagement with the intervention development process, their perceptions of gaps in the market and needs that are not met with existing interventions as well as their perspective of any regulatory gaps that may exist
- Interviews with advocacy groups were tailored based on the work of the organisation to better understand the challenges the individuals they represent face, and the challenges they are hoping to address through their advocacy work.

Table 5 Number of stakeholders contacted per stakeholder group and interviews conducted

Stakeholder group	Number of stakeholders contacted	Interviews conducted
Developers	107	26
Regulators and policymakers	32	6
Investors and funders	35	12
Healthcare providers	24	10
Advocacy groups	13	3
Total	**211**	**57**

Source: Technopolis

2.1.2.2 Prioritisation workshop

A virtual prioritisation workshop was held to review the emerging findings from the study and engage representatives from multiple stakeholder groups to discuss and prioritise challenges in the mental health R&D ecosystem. Overall, 35 participants joined the workshop out of a total of 95 invited. Prior to the workshop, participants were provided with a briefing note outlining key barriers delaying or stopping the development of mental health interventions that had been identified in our literature review and stakeholder consultation. Additionally, they were invited to complete a survey to prioritise the barriers they deemed the most significant to delaying or stopping the development of mental health interventions. Results from the survey were presented at the workshop and breakout sessions facilitated further discussion to build consensus around high-priority barriers and discuss feasible solutions. Following breakout discussions, participants were invited to complete a survey to re-prioritise barriers. Appendix F presents an overview of workshop participants by stakeholder group and their distribution across the different breakout sessions.

2.1.2.3 Validation workshop

A virtual validation workshop was held with participants composed of developers of solutions and the study's expert advisors to discuss the study's findings around barriers and solutions, and a first set of recommendations. During this event, participants were presented with and asked to reflect on the evidence emerging from the study. Secondly, they were asked to review the proposed recommendations to assess their comprehensiveness, appropriateness, feasibility, and transferability to other contexts (i.e. their universalness).

2.1.3 Case studies

A key aim of the study is to understand how developers of mental health interventions make strategic decisions from identifying needs, through investment decisions to initiating and progressing or discontinuing an R&D programme. A total of seven case studies were developed, and sampled across the three intervention types: two pharmaceutical interventions, two medical devices, and three digital therapeutics. The purpose of the case studies is to document the R&D pathways of these interventions.

The specific case studies were identified based on the interviews conducted during stakeholder consultation, focusing on interventions that have reached (or are close to reaching) the market. This is to allow us to capture as comprehensive a picture of the developer's journey as possible. Beyond the developers' perspective, we set out to engage with end users and/or PWLE experts that were involved in the development of the intervention.

2.2 Data Analysis & Triangulation

Four analytical packages were used to conduct the analysis. Each of the analytical packages is presented below detailing the sources of information that fed into the analysis, outlining the synthesis process, and describing the resulting output(s).

2.2.1 Characterisation of the ecosystem

Drawing from the literature review, quantitative data compilation, interviews and case studies, an overview of the relevant mental health R&D ecosystem was created. The framework of the characterisation of the ecosystem provides an organising principle with all data clustered around intervention types, development stages, contextual information, and related learnings. A qualitative synthesis, through deliberative discussions with the expert panel, drew out horizontal lessons, and compared pharmaceutical and non-pharmaceutical interventions. The gaps in the information were explicitly discussed. Where ambiguities were identified between various data strands, we have applied the hierarchy of evidence approach to build the final synthesis. We have used the critical interpretive synthesis approach to combine the results of quantitative and qualitative data analysis. The result of this analysis is presented in Section 4.

2.2.2 Analysis of the decision-making process of developers of mental health interventions

A key aim of the study is to understand how developers of mental health interventions make strategic decisions from identifying needs, through

investment decisions to initiating and progressing or discontinuing an R&D programme. More specifically, this analysis relied on data gathered through direct stakeholder consultation with developers and case studies.

Analysis of the case studies resulted in a generic decision-making process map that captured the logic of developers of pharmaceutical and non-pharmaceutical interventions along the innovation life cycle to approval/accreditation and early uptake (see Section 6). The decision map may help the community to identify critical paths and bottlenecks, and design appropriate support activities to facilitate the development of more mental health solutions in the future.

2.2.3 Prioritisation of universal barriers

From the various data collection activities: systematic literature review, interview with stakeholders, we have identified a longlist of documented barriers. These barriers are organised into a database according to the framework of groupings and attributes: (i) high development costs; (ii) regulatory uncertainty; and (iii) lack of attractiveness of the mental health market to developers, investors, and funders. The database also contains the evidence, both qualitative and quantitative, supporting the barriers. This analytical work package was used to prepare for the prioritisation workshop (Section 1.1.1.1), which resulted in the finalisation of the prioritised universal barriers for each of the three top-level barrier categories.

2.2.4 Identification of solutions

First, the potential solutions were identified and extracted from the literature review resources, targeting the prioritised barriers. Additionally, we conducted targeted desk research to identify additional potential solutions in adjacent areas (i.e. R&D for pain, HIV, antimicrobials, and rare diseases) that can be adapted in the mental health space. These solutions were then triangulated with data from interviews and case studies to identify the most feasible solutions to address the prioritised barriers. The solutions were presented in the validation workshop (see Section 2.1.2.3) with our expert advisors and various developers for an in-depth discussion to validate the potential solutions of the study. Furthermore, we have conducted desk research on existing initiatives in the UK, the US, the EU, Africa, and globally to identify any gaps that these initiatives are currently not addressing. Triangulating our findings of the prioritised barriers, potential solutions, and existing gaps, we have produced a set of recommendations for investors and funders to consider, framing around three main categories of actions: financing, convening, and advocating/influencing.

2.3 Expert guidance

A bespoke expert advisory group was created for the study that represented the necessary expertise in exploring mental health interventions (pharmaceutical, digital and device) and knowledge of the study countries in scope. It was important for the successful delivery of the study to have diversity in the range of expertise,

including lived experience, clinical, regulatory, R&D and innovation.

The following experts supported the study: **Steve Appleton** (President and CEO of Global Leadership Exchange, formerly IIMHL/IIDL, and a board member of the Association of Mental Health Providers in the UK), **Professor James Barlow** (Professor of Technology and Innovation Management in health care systems), **Professor Hugo Critchley** (Professor of Psychiatry at Brighton and Sussex Medical School, University of Sussex and current Chair of Academic Faculty of Royal College of Psychiatrists), **Hayden Holmes** (Health Economist focusing around digital health), **Dr Thomas Kabir** (A lived experience expert, Senior researcher at the University of Oxford, and patient lead for gameChange), **Dr Nicholas Prior** (Practising NHS clinician, with lived experience living with Bipolar, founder and developer of 'Minderful', commitment to equity in Mental Health intervention development), **Claudia Sartor** (Deputy Chief Executive Officer of an international lived experience organisation, the Global Mental Health Peer Network (GMHPN), and a lived experience expert and global mental health advocate fighting for the rights of persons with psychosocial difficulties), **Dr Divya Srivastava** (Health Economist with expertise in digital regulatory landscape in a number of countries and health financing in LMIC settings), and **Professor Karin Waldherr** (A clinical and heath psychologist with a focus on evaluation and implementation research, health promotion, prevention and treatment of mental illness across the lifespan, and Digital Mental Health, and the Head of Institute of Health Sciences at Ferdinand Porsche FERNFH). The advisory group also included specialist technical expertise conducting systematic literature reviews: **Dr Farhad Shokraneh** (information specialist with methodology-based publications in the field of mental health).

The expert advisors in this study were engaged in a strategic and collaborative manner, each contributing their expertise at key stages of the project. Through individual meetings tailored to their specific areas of knowledge, these experts offered insights and guidance crucial to the study's progress. They also participated in broader team meetings to ensure alignment and efficiency across all activities. While each expert had designated points of engagement, they were invited to participate in pivotal activities such as stakeholder mapping and validating recommendation. Additionally, their involvement extended to reviewing data collection tools, co-facilitating workshops, and participating in analytical tasks. This structured approach ensured that the contributions of each expert were maximised and integrated into the study's deliverables.

2.4 Limitations

The study findings are subject to several limitations that may impact the strength of the conclusions. Firstly, stakeholder engagement for data collection posed challenges. Despite efforts such as personalised reminders and support from Wellcome, individuals from pharmaceutical companies were hesitant, unavailable,

or too busy to participate in our consultations. Consequently, case studies included only one conventional pharmaceutical intervention, with psychedelics as the alternative pharmaceutical intervention case study, leading to an imbalance in the perspectives represented in the developer's decision mapping component.

Secondly, missing quantitative data is another key limitation of our study. Datasets provided for analysis only had partial coverage of data on the reasons for clinical trial termination. Around 108 from 375 (29%) terminated pharmaceutical clinical trials did not provide information on the reasons for trial terminations. This gap in information may potentially lead to biased conclusions based on a reduced sample of trials. Similarly, there is missing data in the market size estimates as companies with larger drug portfolios generally only report individual drug sales for their top grossing drugs and will typically group remaining drug sales into 'Other Pharma' sales. Another key example of missing data is the overall poor reporting of clinical trials for digital and non-digital device, as well as the lack of available information on the LoA for medical devices. Consequently, the lack of complete data can result in varied coverage of drug sales within market analysis estimates, impacting the overall accuracy and completeness of the quantitative analysis.

Thirdly, the data coverage is skewed towards larger countries. While GlobalData's marketed devices database officially covers 32 countries, the primary focus is on products approved by regulatory authorities in larger markets, such as the US, Australia, Japan, and China. The coverage for the remaining 28 countries is comparatively more limited. Similarly, the issue of skewness is evident in the country-specific disease burden analysis, with superior data coverage for the United States compared to more limited data availability for South Africa.

3 Typology of mental health interventions

A typology of mental health therapeutic interventions presents an organising framework and structure for examining the mental health R&D ecosystem. This includes comparing the R&D 'journeys' of different interventions and identifying challenges that are common across all types of therapeutic interventions.

Therapeutic interventions are divided into two broad categories, 'pharmaceuticals' and 'non-pharmaceuticals'. These categories are broken down into sub-groups; for example, the first level category 'non-pharmaceuticals' is divided into second level categories 'devices' and 'behavioural' interventions, with 'devices' further subdivided into third level categories 'digital' and 'non-digital'. Due to their distinct technological characteristics, second and third level divisions tend to align with different regulatory pathways and requirements. Further levels of the typology provide more specific subdivisions for each intervention type within their field.

The typology of interventions is presented diagrammatically in Figure 1. In the narrative, we provide definitions for each type of intervention and selected sub-classifications that are within the scope of this study. While categories are set out separately for clarity, it should be recognised that there are instances of overlap, especially in the case of combination products.

This study focuses on **pharmaceuticals**, **digital devices**, and **non-digital devices**; the category 'behavioural interventions' and its subdivisions are outside the scope of this study.

3.1 Pharmaceutical interventions

Pharmaceutical interventions are defined as special preparations used in modern and traditional medicine, essential for the prevention and treatment of diseases, and the protection of public health, drawing from the WHO definition.[5]

Within pharmaceuticals, established or long-standing psychotropic medicines that have effects on psychological function have been classified as **traditional psychotropics**,[6] and further subclassified – using a commonly accepted framework – into antidepressants (e.g. SSRIs, esketamine, MAOIs, and tricyclics), anxiolytics (anti-anxiety medication such as beta-blockers and benzodiazepines), anti-psychotics ('typical' or 'atypical'), and mood stabilisers.[7]

More recently developed pharmaceutical interventions with unique mechanisms of action (MoA) or different pharmacokinetic properties compared to existing treatments are classified as **novel agents**. These include psychedelics, glutamate modulators, cannabinoid receptor modulators and hormonal therapies.

Pharmaceutical interventions initially developed for a non-mental health condition that subsequently proved effective in mental health are classified as **repurposed agents**. Due to the

existence of relevant prior evidence, repurposing adds additional health benefits for patients at lower development costs and shorter timelines.[8] This category represents a diverse group of pharmaceuticals with different MoAs and initial target indications, and are therefore not subclassified further. Examples of repurposed agents for treating mental health conditions include anti-inflammatories (cytokine inhibitors and non-steroid anti-inflammatory drugs, a type of statins prescribed for high blood pressure), L-type calcium channel antagonists (typically used for high cholesterol) and biguanides (specifically Metformin[9] for diabetes).[10] The repurposed agent category also includes ketamine, which is currently used as an anaesthetic but is also considered for treating depression.

3.2 Non-pharmaceutical interventions

3.2.1 Devices

A medical device encompasses a broad range of items, including hardware (e.g. instruments, machines, implants, and materials) and software, designed by manufacturers for medical use either alone or in combination, drawing from the WHO definition.[11] These are further subdivided into 'digital therapeutics' (e.g. app or web-based interventions) and more traditional device-based 'non-digital' interventions (e.g. electric stimulation such as electroconvulsive therapy).

3.2.1.1 Digital therapeutics

Digital therapeutic interventions are defined as evidence-based therapeutic interventions driven by software to prevent, manage, or treat a medical disorder or disease.[12,13] To be classified as a digital therapeutic in the scope of this study, an intervention must meet the definitions and core principles defined by the Digital Therapeutics Alliance:[14]

- Prevent, manage or treat a medical disorder or disease
- Produce a medical intervention driven by software
- Incorporate design, manufacture and quality best practice
- Engage users in development and usability processes
- Incorporate patient privacy and security protections
- Apply deployment, management and maintenance best practices
- Publish trial results inclusive of clinically meaningful outcomes in peer-reviewed journals
- Be reviewed and cleared or certified by regulatory bodies as required to support product claims of risk, efficacy and intended use
- Make claims appropriate to clinical evaluation and regulatory status
- Collect, analyse, and apply real-world evidence and/or product performance data

Digital therapeutics can be subdivided based on specific technological features, often falling into more than one group. Categories include sensor-based and wearable devices, app-based devices, machine learning/AI approaches, virtual reality (VR) platforms (e.g. exposure therapy) and web-based operations (e.g. remote therapy and online support groups). These intervention types can also be categorised based on whether they are

delivered through the presence of a trained health practitioner ('**supported**'), or if patients/users rely mainly on the technology itself ('**unsupported**').

3.2.1.2 Non-digital therapeutics

The non-digital category includes medical devices which are defined by NHS England as 'any instrument, apparatus, appliance, implant, reagent, material, or other article intended by the manufacturer to be used, alone or in combination, for human beings'.[15]

For the treatment of mental health conditions, medical devices typically alter brain activity by applying electrical or magnetic stimuli.[16] Therefore, non-digital medical devices are further subclassified according to the type of stimulating field: '**magnetic stimulation**' and '**electric stimulation**' These 'neurotechnologies' enable the direct connection of technical components with the nervous system.[16] Typically, neurotechnologies are applied for treatment-resistant symptoms[m] or where symptoms require an acute de-escalation, where symptoms need to be reduced rapidly.[17]

3.3 Combination therapies

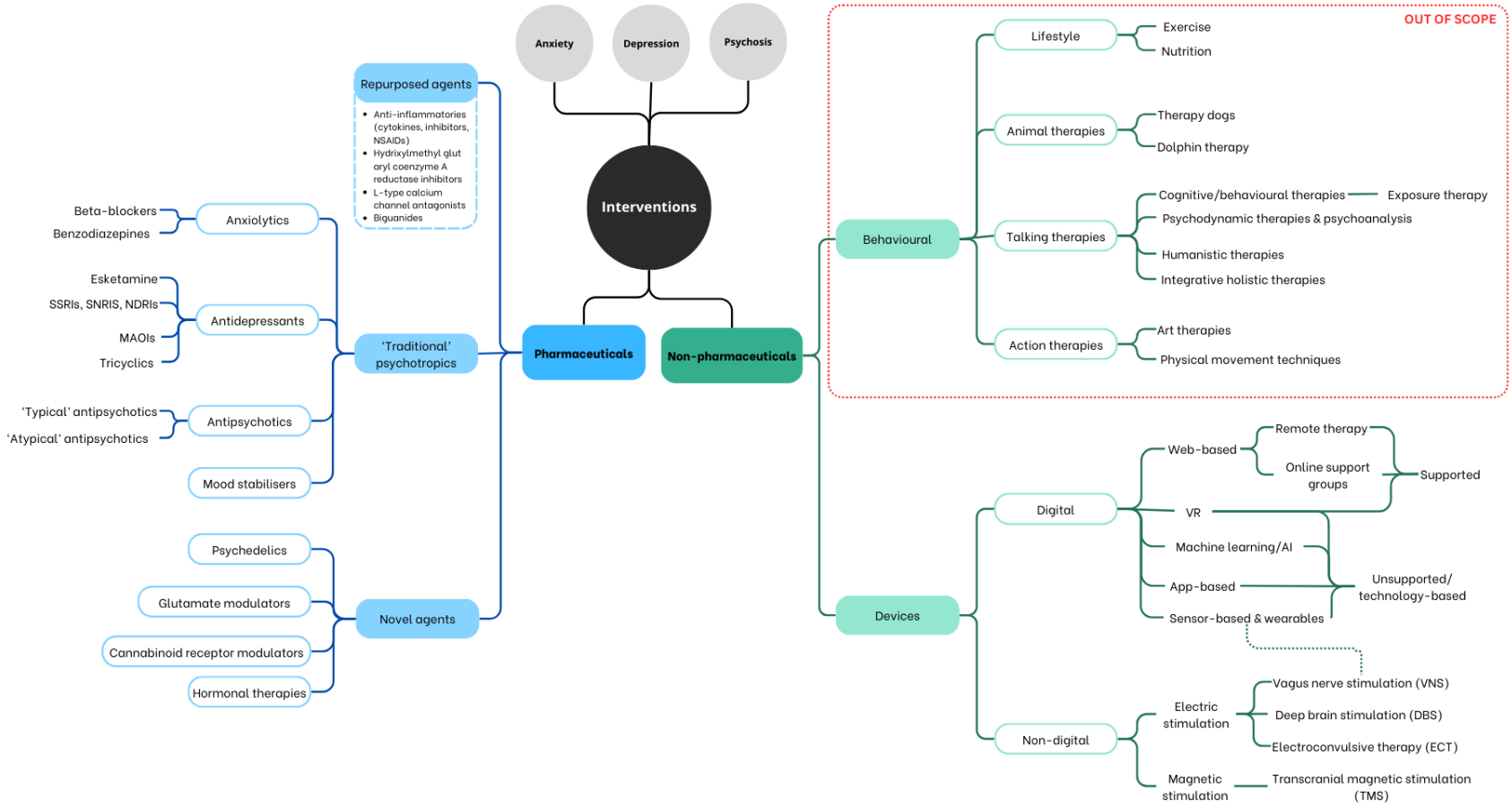
Combination therapies involve two or more types of interventions to increase treatment effectiveness. Examples of combination therapies are:

1. The use of pharmaceuticals in combination with digital devices, e.g. sensor-equipped digital pills to treat patients with schizophrenia, bipolar, or depression,[18] and mobile applications to support consistent intake of drugs as part of the treatment, ensuring intake of medications to drive adherence.[19]
2. A combination of digital and non-digital devices, e.g. a wearable device that provides both vagus nerve stimulation (VNS) and deep brain stimulation (DBS), combined with a digital companion app and the option to incorporate behavioural therapy.
3. Devices (mostly digital) in combination with behavioural therapies, e.g. a web-based remote therapy with unsupported applications featuring exercises derived from cognitive behavioural therapy (CBT),[20] or using virtual reality (VR) applications for exposure therapy (a specific form of CBT).[21]

In this study, combination therapies are classified based on the regulatory pathway(s) that apply to them.

[m] Persisting or worsening mental health symptoms that do not respond to standard treatment approaches, such as pharmaceuticals or talking therapies.

Figure 1 Typology of Mental Health Interventions



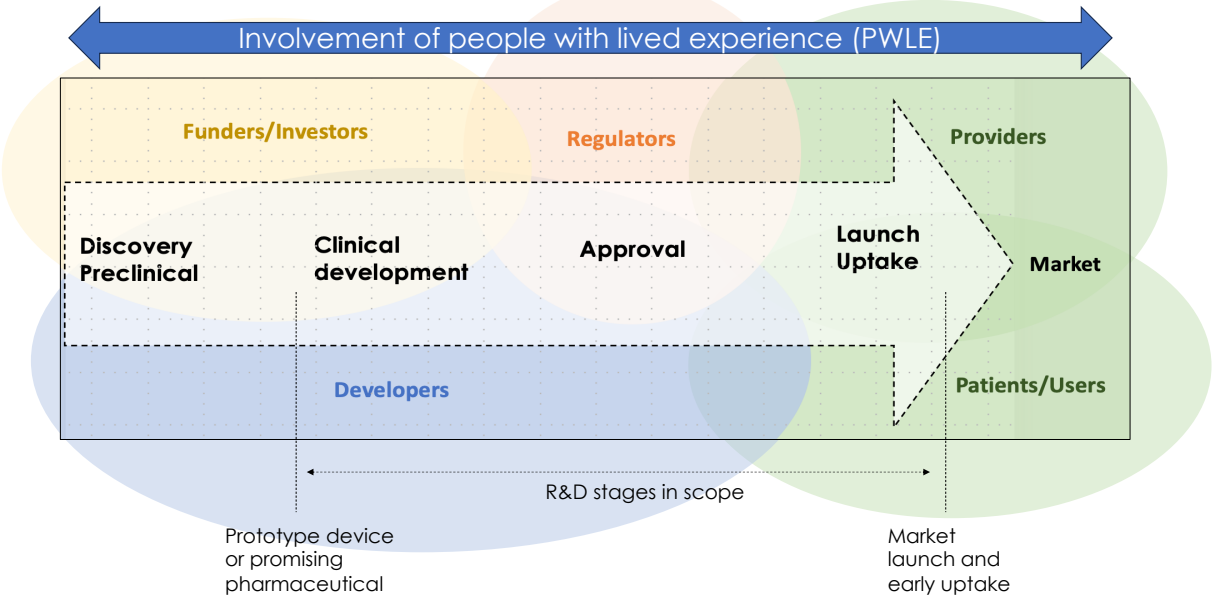
Source: Technopolis

4 Characterisation of the mental health R&D ecosystem

The mental health research and development (R&D) ecosystem involves a range of key stakeholders (Figure 2). Developers drive innovations forward along a complex R&D pathway, with funders and investors, regulators, healthcare providers, patients/users, and people with lived experience each playing a critical role at the different R&D stages.

These stakeholder groups thus shape the decision-making processes followed by developers of mental health interventions. This study focuses on R&D stages from proof-of-concept or prototype of an intervention to market launch and early access, exploring developers' decision-making and barriers to progress along the R&D pathway.

Figure 2 Research and Development Ecosystem



Source: Technopolis

The following sections provide an overview of the mental health R&D ecosystem.

We start with an outline of R&D pathways of mental health innovations, where relevant highlighting differences between the different types of mental health interventions (Section 4.1). This includes a description of key stakeholder groups in the R&D ecosystem, with a focus on regulators in four countries: the US, UK, Germany, and South Africa. We then present an analysis of mental health innovations' progress along the R&D pathways (the 'pipeline').

4.1 R&D pathways for different types of mental health interventions

4.1.1 Overview

The stages of the R&D pathway are as follows:

- **Discovery research:** Exploratory investigations aimed at uncovering novel scientific insights and developing new hypotheses and methodologies, often curiosity-led and mostly conducted by academic researchers. This phase of research is characterised by a broad and open-ended exploration of physiological and disease pathways.[n]
- **Pre-clinical development**: Investigative phase of comprehensive laboratory studies aimed at establishing a scientific foundation ahead of human testing. For pharmaceuticals, it involves computational, *in vitro* experiments and *in vivo* studies in animal models, assessing pharmacodynamic and pharmacokinetic properties of drug candidate molecules and their toxicity profile. Pre-clinical development of devices involves bench studies, animal experiments and simulations, focusing on understanding the functionality, biocompatibility, and potential risks of the innovation.
- **Clinical development:** Clinical trials are conducted with human participants to gather data on the safety and efficacy of new interventions. Typically, earlier trials for pharmaceuticals focus on safety, dosage, and possible side effects, while later-stage trials focus on efficacy and effectiveness at scale. For devices, trial phases are less defined and more variable but may include design, usability, and performance assessment in controlled clinical settings at the early stage and then in broader populations at a later stage.

  Clinical trials generate crucial evidence for regulatory approval and health technology assessment which in turn inform healthcare policy and decision-making. Randomised controlled trial (RCT) methodology is the gold standard to test the effectiveness of a new intervention or treatment compared with other treatment(s), sham treatment (placebo), or no treatment. 'Blinding' participants, data collectors and assessors in a clinical trial (i.e. conceal knowledge of which trial participants received the intervention) is an important methodologic feature to reduce outcome bias.
- **Regulatory approval:** Every country has its own regulatory authority and framework of rules and requirements that must be met before new health interventions can enter the market. In each framework, the nature of the intervention and its associated risk broadly dictate which regulatory pathway is required for its approval.

[n] Discovery research is out of scope for this study and is not further elaborated.

The R&D pathway developers select for an intervention is required for its approval and is inherently tied to the evidence requirements developers have to meet, with the exception for digital therapeutics apps, where developers may choose the well-being market, and thus, skip the regulatory approval stage.

- **Market launch and uptake:** Once regulatory approval has been granted, decisions about pricing and reimbursement take place by going through a health technology assessment (HTA), typically at the national or regional level. These consider the potential role and use of the new intervention in the context of the national health system of that country and involve complex negotiation processes between the marketing authorisation holder (e.g. a pharmaceutical company) and the payer (e.g. a health insurance fund or national health service).

Table 6 provides a list of regulatory and HTA body(ies) for each country in scope of the study.

These stages of R&D pathway described above are intended to serve as milestones in a R&D framework. The distinct characteristics and differences between the R&D pathways of pharmaceuticals, non-digital medical devices, and digital therapeutics are discussed in Section 1.1.1 and Section 4.1.3.

Table 6 Regulatory and HTA body(ies) for each country in scope of the study

Country	Regulatory body
UK	Medicines and Healthcare products Regulatory Agency (MHRA), National Institute for Health and Care Excellence (NICE)
Germany	Federal Ministry of Health (BMG) in collaboration with the Federal Institute for Drugs and Medical Devices (BfArM), IQWiG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; Institute for Quality and Efficiency in Healthcare)
European Union	European Medicines Agency (EMA)
United States	Food and Drug Administration (FDA)
South Africa	South African Health Products Regulatory Authority (SAHPRA)[o]

4.1.2 Pharmaceuticals

In the development of pharmaceutical interventions, lead candidates enter pre-clinical development studies (*in vitro* and *in vivo* experimental models) to obtain preliminary pharmacokinetic, efficacy, toxicity, and safety information.

[o] Regulatory processes in many African countries including South Africa are not well-defined, and countries may rely on clearance from the EMA or FDA.

If pre-clinical testing of a drug candidate shows promise, the developer has to apply to the relevant regulatory body to progress its development and move into clinical trials. As noted earlier, the gold standard of study design for clinical trials is the RCT methodology. Approval to commence a clinical trial relies on a favourable assessment by a research ethics committee (REC), who must judge that the trial is sufficiently well designed, that the pharmaceutical intervention under development has clinical and social value, and that safeguards to protect participants are in place such that the potential benefits of the trial outweigh the risks. Clinical trials are divided into a series of phases that each require approval from REC to proceed (see Table 7).

Table 7 Overview of clinal trial phases for pharmaceuticals

Phase	Participants	Purpose
Pilot	<20	Test a very small dose of a new drug in healthy human participants to study its effects on the body, often referred to as microdosing studies. Not all drugs undergo this phase.
I	20–100	First human study to test the safety, toxicity, and dosage of the new drug, usually in healthy human participants.
II	Up to 100s	Assesses the efficacy and safety (incl. side effects) of new therapy in patients with the disease/conditions.
III	300–3,000	Confirms clinical efficacy and safety (i.e. any adverse reactions) in patients. Provides the primary basis for the benefit–risk assessment for the new therapy.
IV	1,000s	Monitors long-term (post-authorisation) effectiveness and safety (including side effects, also called pharmacovigilance) of the drug in general population in real-world conditions.

Source: https://www.fda.gov/patients/drug-development-process/step-3-clinical-research; Sambandan *et al*. (2019)[22]

All pharmaceutical interventions must undergo clinical trials to demonstrate they are safe and effective before they can be approved for use (regulatory approval). The developer then submits an application for **market authorisation** to the regulatory authority, providing evidence that the therapeutic intervention is effective, safe and meets manufacturing quality standards. If the regulatory authority is satisfied, a marketing authorisation is issued, allowing the developer to sell or supply the product to end users.

In the UK, pharmaceuticals are regulated by the Medicines and Healthcare products Regulatory Agency (MHRA) under the Human Medicines Regulations 2012 (SI 2012/1916), which has recently been amended to reflect the UK no longer

being part of the EU licensing system, and thus, pharmaceuticals to be marketed in Great Britain and Northern Ireland will now be required to be authorised via UK national route.[23]

In the US, pharmaceuticals are regulated by Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act.[24]

In Germany, pharmaceuticals are regulated by the European Medicines Agency (EMA), under the EU legal framework for human medicines, which sets standards to ensure a high level of public health protection and the quality, safety, and efficacy of authorised medicines. The requirements and procedures for marketing pharmaceuticals are laid down in Regulation (EC) No 726/2004,[25] currently under revision.[26] The EMA can grant market authorisation across EU countries via the centralised procedure. The Division Safety of Medicinal Products and Medical Devices, part of the Federal Institute for Drugs and Medical Devices (BfArM), is responsible for the authorisation of medicines available in Germany that do not pass through the centralised EU procedure.[27]

In South Africa, pharmaceuticals are regulated under the Medicines and Related Substances Act, 1965 (Act No. 101 of 1965), which was last amended in 2015 and enabled the establishment of the South African Health Products Regulatory Authority (SAHPRA) to oversee the regulation of pharmaceuticals.[28]

Pricing and reimbursement decisions involve complex negotiation processes between the seller (e.g. a pharmaceutical company) and payer (e.g. a health insurance fund or national health service) to balance multiple conflicting goals, such as ensuring medicines are affordable for healthcare systems while also being profitable for companies.

The **UK, US,** and **Germany** have implemented **health technology assessments (HTA)-based evaluation** which appraises the clinical and cost-effectiveness of interventions in order to guide pricing and reimbursement decisions and support uptake of the most effective treatments. **In the UK**, the National Institute for Health and Care Excellence (NICE) develops this guidance. The equivalent to NICE **in Germany** is the Quality and Efficiency in Healthcare (IQWiG). **In the US**, the Institute for Clinical and Economic Review (ICER) is emerging as the national body influencing pricing and reimbursement decisions.[29] Instead, each private and public payer makes its own coverage decisions and conducts its own price negotiations.[30]

South Africa has a commitment to implementing HTA processes through the establishment of National Health Insurance (NHI), however, a formal national HTA process has yet to be established. Currently, both public and private healthcare sectors employ elements of HTA to varying degrees, with institutions such as National and Provincial Departments of Health, National Treasury, National Health Laboratory Service, Council for Medical Schemes, medical scheme

administrators, managed care organisations, academic or research institutions, clinical societies and associations, pharmaceutical and device companies, private consultancies, and private sector hospital groups involved in HTA or related activities to inform access and resource allocation decisions.[31]

4.1.3 Devices

Medical devices (digital and non-digital) undergo testing after an initial design, known as a prototype, has been developed. At the pre-clinical stage, prototypes are tested in controlled laboratory settings to refine and de-risk the design.

Many regulatory authorities employ a risk-based classification system to determine whether a medical device or digital therapeutic requires further testing in clinical trials.[32] Medical devices and digital therapeutics classified as low risk are not required to provide clinical data. For those interventions classified as higher risk, clinical trials may be required. In this case, the developer needs to submit an application to the regulatory authority to move forward. Clinical trials that test devices broadly follow the same phases as clinical trials of pharmaceutical interventions. As for pharmaceuticals, RCTs are considered the gold standard for clinical trials evaluating medical devices and digital therapeutic interventions. Table 8 shows the simplified clinical trial phases for devices.

Table 8 Overview of main clinical trial phases for medical devices[p]

Phase	Participants	Purpose
Pilot	10–30	Small study to determine safety and performance
Feasibility study	20–30	Larger study to assess efficacy, safety and adverse effects
Pivotal	100s	Large study to confirm clinical efficacy, safety and risks
Post-market	1000s	Monitors long-term effectiveness and safety in general population

Source: https://genesisresearchservices.com/clinical-trials-medical-device-trials/

In addition to market authorisations, manufacturers of digital (digital therapeutics, classified as software as a medical device) and non-digital medical devices that require clinical testing must also **declare conformity**

[p] Other types of trials include adaptive trials, combined phases, and sub-stages (2A/B) depending on the design. Only in some cases do regulatory authorities require Phase IV trials/post-market trials, which is often the case when there are limited numbers of patients in Phase I-IIII trails.

before the product can be placed on the market. This process involves demonstrating that the device meets specified safety, performance, and quality standards as mandated by regulatory authorities. Various standards can be used to show conformity, e.g. the international standard ISO 13485 which covers quality management systems throughout the life cycle of a medical device, from initial conception to production and post-production.[33]

For medical devices (digital and non-digital) to be marketed in **Europe**, a CE mark must be obtained, confirming the device meets high safety, health and, where possible, environmental standards.[34,35] This was also the case for devices in the **UK** until the CE mark was replaced with the UKCA marking in June 2023.[35] For medical devices classified as low-risk, manufacturers can self-certify against CE/UKCA marking, whereas devices classified as higher risk must go through a conformity assessment by an EU/UK approved body.

The US takes a different regulatory approach that assesses both the effectiveness and the risk of harm associated with a medical device.[36] Low-risk medical devices fall under the 510(k) pathway (pre-market notification), which requires manufacturers to prove the device is substantially equivalent to a similar existing product already on the market. Higher-risk medical devices fall under the PMA (pre-market approval) pathway that requires demonstrating the safety and effectiveness of a new device for end users. This typically requires the submission of data from both pre-clinical and clinical studies.

South Africa has also adopted a risk-based classification system for medical devices.[37] All classes of medical devices require a valid 'SAHPRA medical device establishment licence' before they can be manufactured, distributed, or sold.

4.1.3.1 Digital therapeutics

In recent years, digital therapeutics have emerged as a novel intervention type in mental health. This has however created challenges for regulators as existing regulatory processes and expertise are not fully adapted to the characteristics of digital therapeutics (e.g. software updates, modifications based on artificial intelligence/machine learning).[38] Moreover, regulatory pathways for digital therapeutics are often unclear and vary across different jurisdictions.[38,39] This could be due to a combination of factors. Firstly, the field is relatively new and rapidly evolving, presenting a challenge for regulatory bodies to keep pace with technological advancements and iterative product development cycles. Additionally, there may be a lack of personnel with expertise specifically tailored to regulate digital therapeutics, further complicating the process. These factors may mean that new, bespoke regulatory processes tailored to the unique nature of digital therapeutics may be needed.

To harmonise regulatory practices for digital therapeutics around the world, the International Medical Device Forum (IMDRF), a consortium of medical device regulators from around the

world, was established.[40] Through the IMDRF, regulators have reached a consensus on a definition for this category of interventions, 'software as a medical device' (SaMD) as 'software intended to be used for one or more medical purposes that perform these purposes *without being part* of hardware medical device'. SaMD differs from 'software in a medical device' (SiMD) in that it performs a medical function in itself (e.g. interpreting magnetic resonance imaging data) as opposed to being integral to the function of a piece of hardware (e.g. turning an MRI machine's magnet). The IMDRF develops guidelines which can be adopted and adapted by member countries (which include the US and the European Union) to inform their own regulations.

As for all medical devices, SaMD interventions may be subject to regulation depending on their risk classification.

In the **United States**, SaMD products are regulated through existing approaches used to approve lower-risk medical devices (e.g. *de novo* and 510(k) pathways). The *de novo* process typically applies to novel low-risk medical devices (e.g. software supporting patients to maintain coping skills or engage in behavioural techniques such as CBT) and requires reasonable assurance of safety and effectiveness for the intended use. If sponsors can show substantial equivalence to one or more products already on the market, they can submit a 510(k) application, which does not require additional safety or efficacy data. The FDA published the 'Software as a Medical Device: Clinical Evaluation final guidance' in 2016, providing an initial framework to help further development of specific regulatory approaches and expectations for regulatory oversight of digital therapeutics.[41]

In the UK, medical devices are regulated under the Medical Devices Regulations 2002 (SI 2002 No 618, as amended), known as the UK MDR 2002.[34] The MHRA published guidance on 'Software and AI as a Medical Device Change Programme – Roadmap' in 2022,[42] which covers a wide variety of regulatory issues for all SaMD, from classification through to access and monitoring, and aims to ensure patient safety while instilling clarity for developers.

In the EU, the European Commission published guidance in 2019 that defines the criteria for the qualification and classification of software as a medical device or *in vitro* diagnostic medical device, based on factors such as intended use, risk level, and mode of action. It aims to ensure consistency and clarity in the regulatory process for software products, facilitating compliance with the requirements set forth in the Medical Device Regulation (MDR) and In Vitro Diagnostic Medical Device Regulation (IVDR).[43]

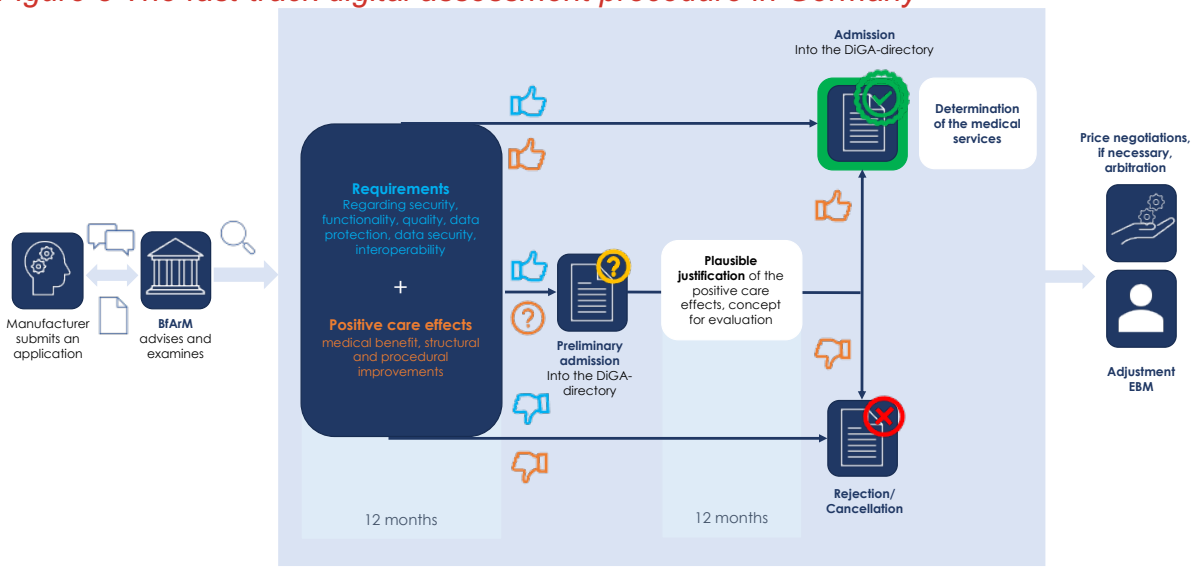
Germany was the first country to introduce a 'fast-track' pathway for digital therapeutics[44] in 2019 to encourage digital innovation and accelerate the regulatory process.[45] Figure 3 shows the DiGA fast-track procedure for digital therapeutics. The DiGA fast track process not only offers an expedited route for regulatory

approval of digital health applications, it also facilitates quicker access to reimbursement under statutory health insurance. This accelerated pathway prioritises digital health technologies, ensuring timely availability for patients while upholding stringent standards for safety, efficacy, and data privacy.[46]

South Africa is currently developing regulations for digital therapeutics. In 2019, the 'National Digital Health Strategy for South Africa' was published which sets out a strategic aim to 'formulate a national legislative, policy and regulatory framework for digital health'.[47]

In addition to the regulated healthcare market for clinically diagnosed mental health conditions, digital products deemed to pose no risk under the regulators' risk-classification system can enter the consumer 'well-being' market largely unregulated.

Figure 3 The fast-track digital assessment procedure in Germany



Source: Adapted from https://www.bfarm.de/EN/Medical-devices/Tasks/DiGA-and-DiPA/Digital-Health-Applications/Interesting-facts/_node.html

4.2 Progression along the R&D pathway – the mental health innovation pipeline

4.2.1 Overview

Innovation can play a fundamental role in the success and long-term survival of a business. Whether in the form of a novel product or service, or an improved production or organisational process, innovation can give businesses an edge over other competitors that can materialise in greater market shares and/or revenues. In healthcare, innovation can be mostly found as the outcome of investing in successful R&D activities that catalyse advancements in medical research and technologies resulting in more effective treatments, diagnostics, and preventive measures. Healthcare innovation is crucial for addressing the ongoing and changing needs within

society, such as the growing prevalence and disease burden of mental health disorders, ultimately leading to improved living standards and increased social and economic welfare for individuals and society, among other positive benefits.

Innovation is a continuous process and, as such, an 'innovation pipeline' can be an effective framework to streamline this process. There is no standard definition for an innovation pipeline, but, generally, this type of framework acts as a useful guide to flow creative concepts through various stages of development, testing, implementation, and commercialisation. In the realm of innovation in mental health interventions (and healthcare in general), this process is not dissimilar to the progressions described in Section 4.1.

For all types of interventions, the pipeline will generally begin with a conception phase (referred to as 'discovery research' and 'pre-clinical development' in Section 4.1). The conception phase is about ideation, identifying what the problem is, brainstorming potential solutions, and narrowing this to those that are most viable and desirable. These ideas are typically followed by a preliminary investigation and scoping studies to validate the understanding and feasibility of the proposed solution. If deemed feasible, the concept can then be developed further by building an initial prototype or minimum viable product (MVP) and testing it in a controlled setting before testing it in the real-world. For pharmaceuticals, in particular, this phase of the pipeline is very much dictated by the regulatory landscape (i.e. it requires to go through defined clinical phases to ensure the safety and efficacy of the drug). Following refinements and demonstrating compliance with existing regulations, the product or service can be launched in the market, which may also require a marketing strategy, scaling up production, and other complementary services to monitor and maintain the new product or service over time. It is important to note that this is a simple representation of the pipeline, and that there is a plethora of external and internal factors that are likely to dictate the decisions made at each stage and whether the concept ultimately materialises into a marketable product or service (see Section 7 on barriers in the mental health R&D ecosystem, for example).

4.2.2 Pharmaceuticals

We analysed data from *Trialtrove* to gain insights into the pipeline of pharmaceutical products for mental health across the R&D pathway. The dataset contains information on 2,976 pharmaceutical drug clinical trials conducted over the past eleven years (2013–2023), including trials for depression (1,501 trials, 50%), psychosis (1,221 trials, 41%) and/or anxiety (627 trials, 21%).[q] Figure 4

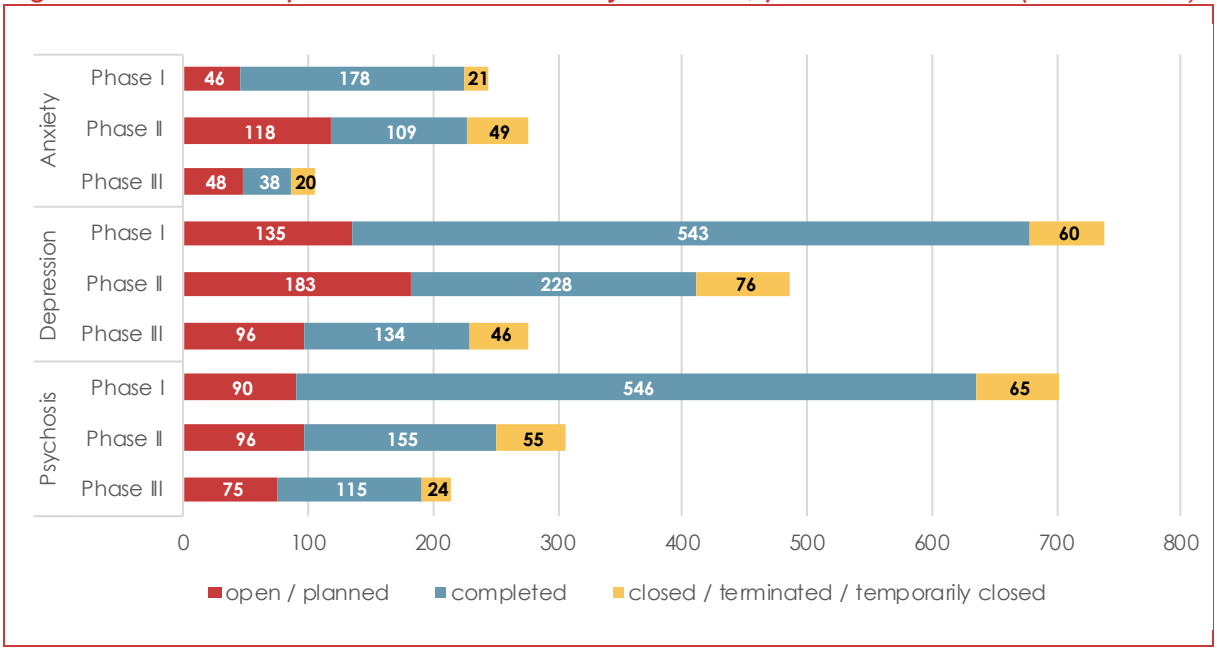
[q] Note the dataset includes clinical trial information for the following indications: **Anxiety** (including body dysmorphic disorder, generalised anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder post-traumatic stress disorder (PTSD), and social anxiety disorder); **Depression** (including major depressive disorder (MDD), postpartum depression, seasonal affective disorder); and **Psychosis** (including bipolar disorder, premenstrual dysphoric disorder, schizophrenia).

indicates that developers have conducted fewer trials for anxiety interventions, despite the higher prevalence and disease burden compared to psychosis conditions, such as bipolar and schizophrenia (see Section 1.1).[48,49]

Around 9% of Phase I clinical trials have terminated (permanently or temporarily) due to challenges encountered in the early-stage development of drug candidates. The percentage of trials that are terminated exhibited a notable increase in Phase II (16%–18%) and Phase III (11%–19%).

Around 57% of all pharmaceutical trials in the dataset received funding from a single source, while the remaining 43% received funding from multiple sources. The predominant sources of funding were identified as industry and academia, with around 59% of trials sponsored by industry (1,744 trials) and 42% of trials by academia (1,245 trials). A slightly smaller proportion of trials (8%, 230 trials) received funding from government and/or non-profit organisations.

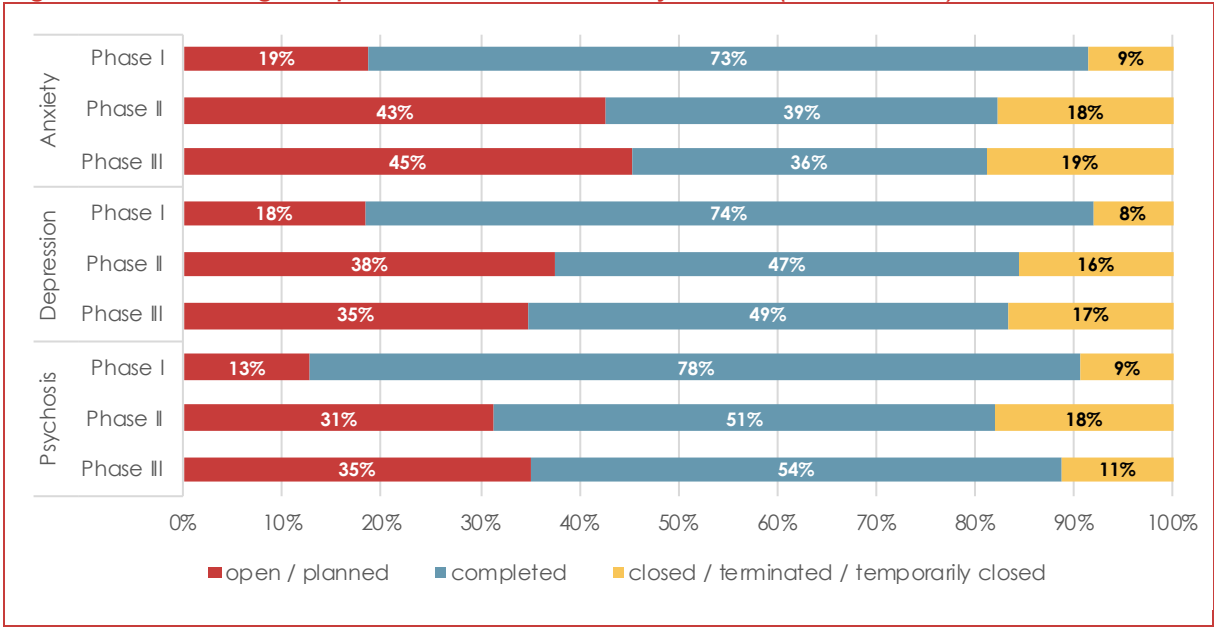
Figure 4 Number of pharmaceutical trials by disorder, phase and status (2013–2023)



Source: Trialtrove, Technopolis analysis. *Note: Clinical trials in the Trialtrove database may contain more than one disease/patient segment.*

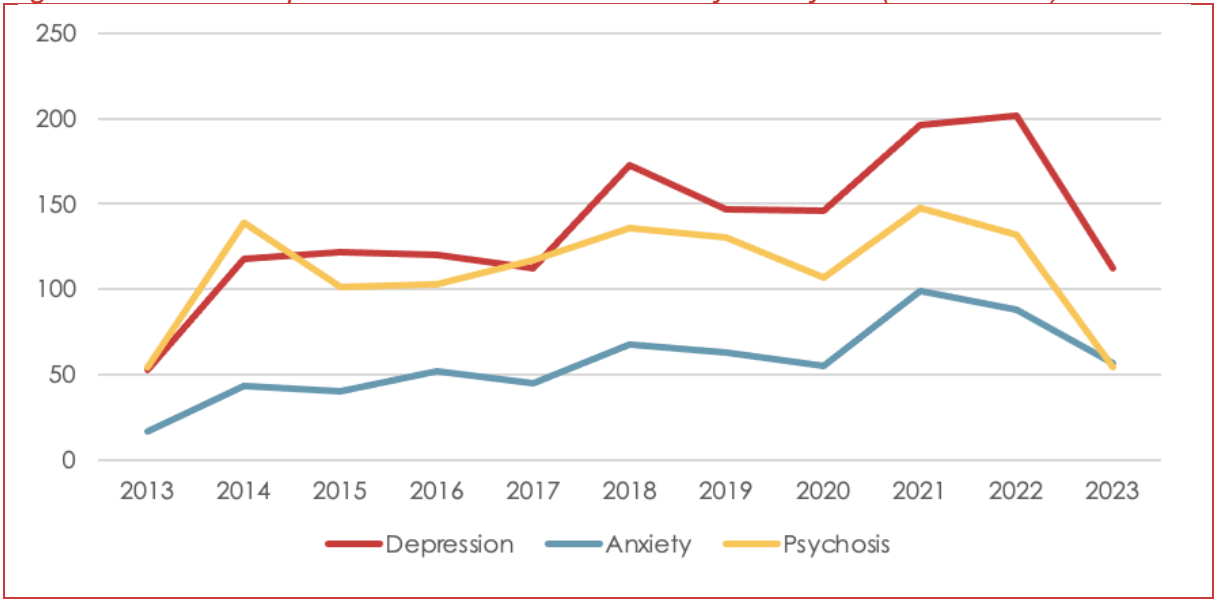
These conditions reflect the categories for which there is data rather than a comprehensive list of conditions in scope of the study. Indications in scope of the study that are not included in the clinical trial analysis include Perinatal anxiety, Persistent depressive disorder, Postpartum psychosis. More information is here: https://www.citeline.com/en/products-services/clinical/trialtrove.

Figure 5 Percentage of pharmaceutical trials by status (2013–2023)



Source: Trialtrove, Technopolis analysis.

Figure 6 Number of pharmaceutical clinical trials by start year (2013–2023)



Source: Trialtrove, Technopolis analysis. *Note: the figures include all trials regardless of status. The figures for 2023 include trials with an anticipated started date.*

The **Likelihood of Approval (LoA),** which shows the likelihood a drug progressing from its current phase to approval, is one important metric of clinical trial success (see Table 9). The analysis indicates that only 10–12% of drug development programmes for depression and psychosis (which includes an average across both bipolar disorder and schizophrenia) successfully transition from Phase I to

market approval.[r] The probability of approval increases as drug candidates progress through the phases of clinical trials. Notably, the two mental health conditions have the same or higher LoA across all phases, compared to drug development programmes for psychiatry and the average for all indications overall.

Table 9 Likelihood of Approval (LoA)

	Anxiety	Depression	Psychosis	Psychiatry	All Indications
Phase I to approval	No data available for this study	11%	11%	7%	8%
Phase II to approval		15%	21%	14%	15%
Phase III to approval		53%	65%	51%	52%
Application for regulatory approval to approval		96%	97%	91%	91%

Source: Citeline Datamonitor Healthcare reports for depression, bipolar disorder, and schizophrenia (for pharmaceutical interventions). The figures for psychosis represent an average of the data for bipolar disorder, and schizophrenia. The figures for the 'psychiatry' and 'all indications' categories were sourced from a separate published report, 'Clinical Development Success Rates and Contributing Factors 2011–2020' report. The estimates for all indications include 15 groupings such as infectious disease, oncology, cardiovascular disease and more (see methodology section for a full list). *Note: application for regulatory approval is defined as a New Drug Application (NDA) or Biologics License Application (BLA). The LoA is calculated as the product of each phase's success probability leading to approval.*

[r] Note that the Datamonitor Healthcare reports were only available for three conditions (Depression, Bipolar Disorder, and Schizophrenia). As such, the LoA analysis was not available for anxiety. The figures for Psychosis represent an average across Bipolar Disorder, and Schizophrenia.

Another important metric is the **Probability of Success (PoS)** which shows the likelihood that a drug advances from its current phase to the next.[s] There do not appear to be strikingly large differences in the PoS for interventions targeting mental health conditions compared to all other indications, as shown in Table 10. One exception to this appears to be for pharmaceutical products for depression, which have a higher probability of advancing from Phase I to Phase II (70%) compared to all other indications (52%), as well as other mental health indications including psychosis (53%). When considering the probability of advancing from Phase II to Phase III, however, the PoS for pharmaceuticals for depression is much lower (29%), but in line with all other indications. For all indications, the higher PoS in the earlier stage of clinical testing (i.e. advancing from Phase I to Phase II) is typically influenced by a focus on safety and the early identification of promising drug candidates, while the transition into later phases (i.e. advancing from Phase II to Phase III) involves more significant challenges related to confirming efficacy in larger and more diverse patient populations.

The transition from Phase III to the submission of an application for regulatory approval also represents a critical junction in the drug development process. The data indicates that more than half of the drugs undergoing Phase III trials for depression successfully progress to the application filing stage for market approval. This is in line with the average PoS for all indications at this stage (58%). The corresponding success rate is approximately 68% for drugs targeting psychosis (which is an average rate for both bipolar disorders and schizophrenia treatments), which appears to be larger than the average for all indications. There may be several factors influencing this revolving around the quality of the evidence generated from the clinical study or trial to demonstrate the drug's efficacy or safety, the barriers to seeking regulatory approval and costs associated with overcoming those barriers, or other ethical concerns. Following this transition, most drugs (>90%) are then approved. The share of unsuccessful transitions at this stage may be attributed to challenges associated with regulatory scrutiny and inspection of the necessary robustness of the clinical trial efficacy and safety. It is not immediately clear why the PoS at this stage appears to be higher for the two disorders, depression and psychosis, compared to psychiatry interventions more generally and all indications.

During the development of an intervention, developers and investors do not receive a financial return on their investment. This can be

[s] The Probability of Success estimates for psychiatry and all indications was sourced from a published report called 'Clinical Development Success Rates and Contributing Factors 2011–2020', https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf The estimates are based on clinical trial data monitoring conducted by Informa Pharma Intelligence's Biomedtracker. This information was then populated into a purpose-built Probability of Technical Success (PTS) tool, Pharmapremia. The same methodology and data sources were implemented to estimate the PoS for Depression, Bipolar, and Schizophrenia. These estimates were provided separately for the purposes of this study.

challenging, particularly for smaller companies that rely on external sources of investment. Our analysis indicates that clinical development timelines for pharmaceutical products to treat mental health conditions vary across different indications. As shown in Table 11, the average clinical research period is 9.6 years for depression and 9.2 years for psychosis (including an average of both bipolar disorder and schizophrenia). This is comparable to an average clinical research period of 10.5 years across all health conditions.

Clinical trial duration can be influenced by multiple factors including prevalence rates of the conditions, time needed to enrol eligible patients, attrition rates and non-adherence to medications, study designs, as well as the speed and efficiency of internal processes of the study team. In addition, later phases are typically complicated by the need to optimise dosing and assess preliminary efficacy, rather than focusing on safety assessments involving smaller samples and shorter durations.[50]

Table 10 Probability of Success (PoS)

	Anxiety	Depression	Psychosis	Psychiatry	All Indications
Phase I to Phase II	No data available for this study	70%	53%	53%	52%
Phase II to Phase III		29%	32%	27%	29%
Phase III to application for regulatory approval		55%	68%	56%	58%
Application for regulatory approval to Approval		96%	97%	91%	91%

Source: Citeline reports for depression, bipolar disorder, and schizophrenia (for pharmaceutical interventions). The figures for psychosis represent an average of the data for bipolar disorder, and schizophrenia. The figures for the 'psychiatry' and 'all indications' categories were sourced from a separate published report, 'Clinical Development Success Rates and Contributing Factors 2011–2020'. The estimates for all indications include 15 groupings such as infectious disease, oncology, cardiovascular disease and more (see methodology section for a full list). *Note: application for regulatory approval is defined as a New Drug Application (NDA) or Biologics License Application (BLA).*

Table 11 Average duration (years) of clinical trials, by phase

	Anxiety	Depression	Psychosis	Psychiatry	All Indications
Phase I	No data available for this study	2.2	2.3	2.3	2.3
Phase II		2.5	2.7	3.4	3.6
Phase III		3.5	2.9	2.8	3.3
Application for regulatory approval		1.4	1.4	1.8	1.3
All		9.6	9.2	10.4	10.5

Note: Citeline reports for depression, bipolar disorder, and schizophrenia (for pharmaceutical interventions). The figures for psychosis represent an average of the data for bipolar disorder, and schizophrenia. The figures for the 'psychiatry' and 'all indications' categories were sourced from a separate published report, 'Clinical Development Success Rates and Contributing Factors 2011–2020' report. The estimates for all indications include 15 groupings such as infectious disease, oncology, cardiovascular disease and more (see methodology section for a full list).

4.2.3 Devices (non-digital)

Data from GlobalData's Clinical Trial Database[t] suggests that between 2013 and 2023, 613 trials involved medical devices for the diagnosis or treatment of anxiety, depression, and/or psychosis. Of these, only 106 (17% of the trials) include information on the trial phase. It is unclear whether this is due to the nature of the medical device R&D pathway as some forms of medical devices may not require going through defined clinical trial phases where the device is considered to be of low or moderate risk, or if it is a lack of information in the database itself. There is no variable in the dataset that contains information on the risk level of the medical device that could provide a more concrete indication on this. Similarly, we are unable to comment on the PoS and LoA for non-digital medical devices due to a lack of information.

Figure 7 illustrates the status (open, completed, terminated) of the medical

[t] The GlobalData database contains information on medical device clinical studies that are conducted across the globe. It covers all medical device trials intended for diagnosis, treatment and management, by individual disease, condition and/or symptom. See: https://www.globaldata.com/industries-we-cover/healthcare/

device trials in the dataset.[u] Most of the trials in the dataset are either open or completed, and only a small portion have been closed or terminated. In accordance with variable definitions, we refer to open trials as trials that are labelled as 'planned' and 'ongoing'. The former is defined as a trial that is open but has not started recruiting patients, and the latter as a trial where patients are receiving an intervention or being examined. Trials that have been 'completed' refer to those that have ended normally and where patients are no longer being examined or treated. Lastly, we refer to a terminated trial as one that has stopped recruiting or enrolling patients early and will not start again, stopped early before enrolling its first patient, or has stopped recruiting or enrolling patients early but may start again.

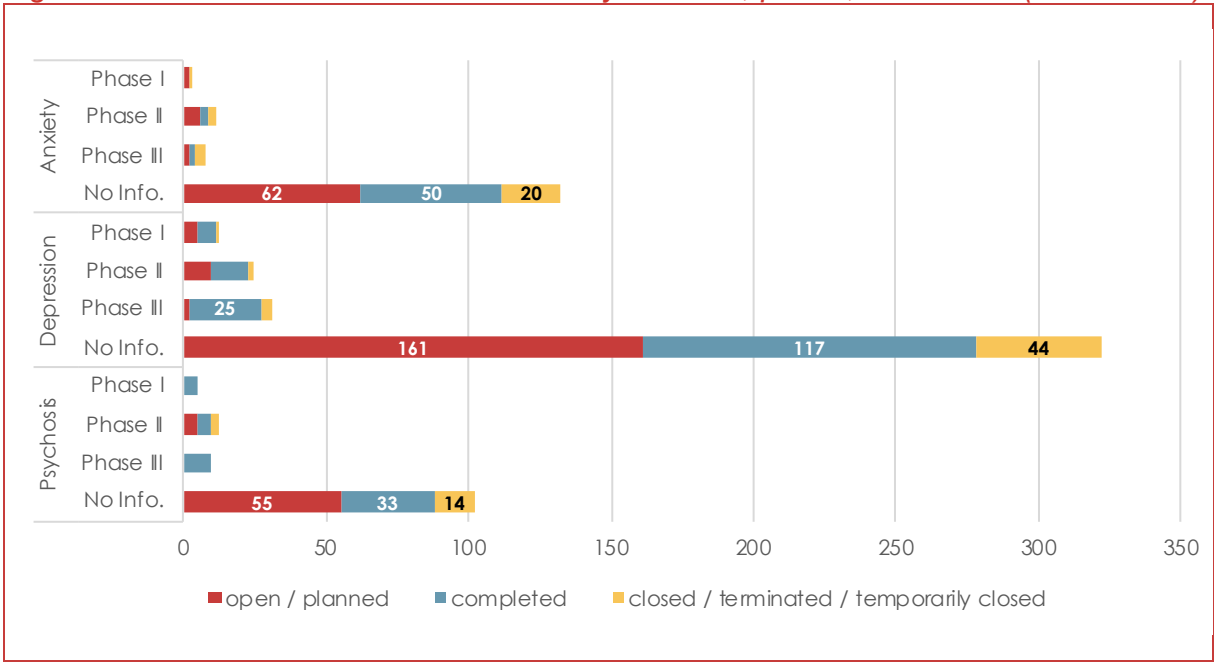
The trials in the database mostly concern devices intended to diagnose, prevent, or treat only depressive disorders (332 out of 613, 54%), followed by medical devices for anxiety disorders (121 out of 613, 20%), and, finally, psychosis (98 out of 613, 16%). There is a small subset of trials for devices intended for a combination of the three disorders: 31 trials for medical devices intended for both anxiety and depression (5%), 29 for depression and psychosis (5%), one for anxiety and psychosis, and one for all three conditions. The last one refers to a clinical study on the efficacy and safety of neuromodulation therapy for the mechanistic treatment of anxiety disorders, bipolar disorders, depression, and post-traumatic stress disorder that is being carried out by the University of Texas (Austin, US).

The differences in number of trials pertaining to the different disorders may be due to several reasons, including market size and value or the feasibility of devices to diagnose/treat depressive disorders, for example.

Of the 599 trials that reported information on their location, just over half are/took place in the US (306 of 599, 51%). This includes single-site trials (290 of 306, 95%), and multiple-site trials (16 of 306, 5%). We refer to the latter as a trial that reported multiple countries regarding the location of the trial site (e.g. United States *and* Canada). Only 19 trials (3.2%) included sites in the UK (considering both single-site and multiple-site trials) and 21 in Germany (3.5%). The rest of the trials in the database with reported site locations include other countries in Europe, North America (Canada, Mexico), South America (Brazil, Argentina, Peru), and Asia (China, Japan, South Korea, India, Malaysia, and the Philippines, among others), and a small number in Africa (four trials with a reported site in South Africa and three trials with a reporter site in Egypt).

[u] In the Figure, Phase I trials include all trials reported to be in Phase 0 and Phase 1; Phase II trials include all trials reported to be in Phase I/II and Phase II; Phase III trials include all trials reported to be in Phase II/III, Phase III, Phase III/IV and Phase IV.

Figure 7 Number of medical device trials by disorder, phase, and status (2013–2023)



Source: GlobalData, Technopolis analysis.

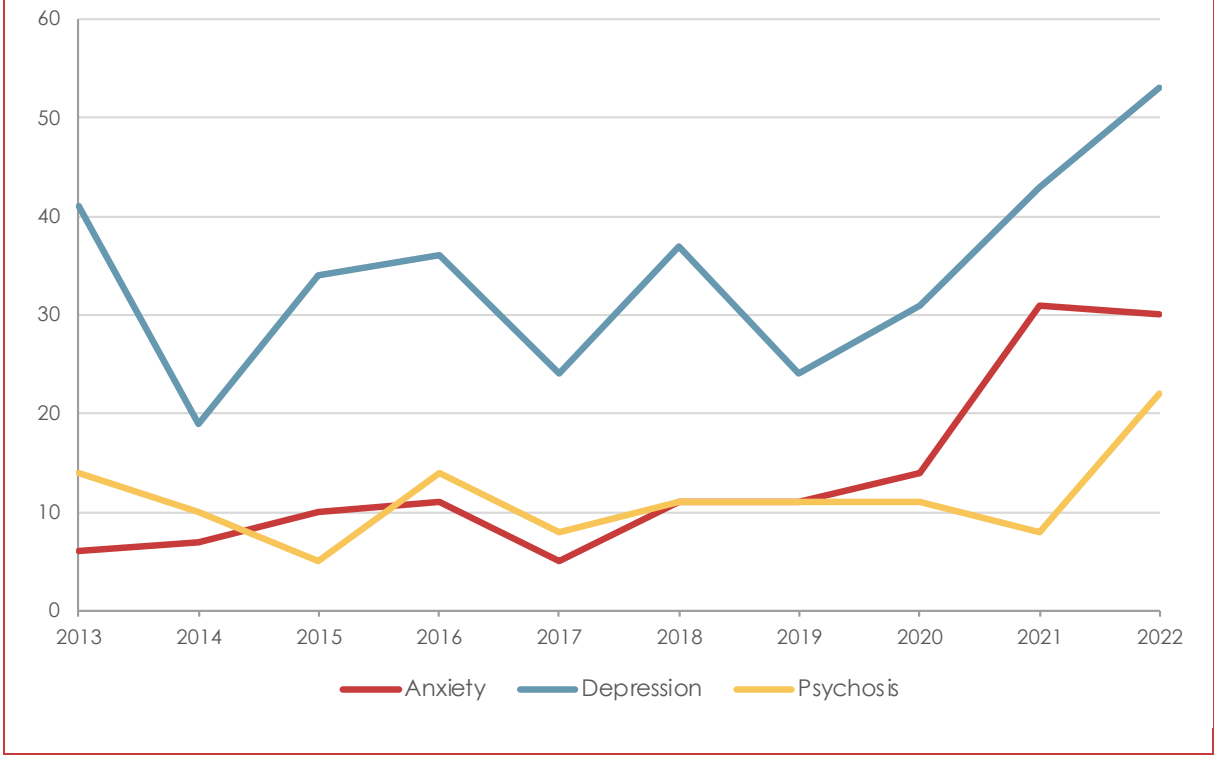
All trials with the UK as a reported site and information on the clinical phase of the study are in Phase III and completed (4 of 19, 21%). This includes, for example, a clinical study on a transmucosal drug delivery device to treat major depressive disorder. The other trials with the UK as a reported site do not have information on the clinical trial phase. These are reported as ongoing (6 of 19, 31%), completed (7 of 19, 37%), and terminated (2 of 19, 11%). A similar reading can be made regarding trials with a reported site in Germany, where those trials with information on their clinical phase are all completed (six in Phase III [6 of 21, 29%] and one in Phase II). For those that do not report on a clinical phase, seven are ongoing (33%), six are completed (29%), and one is terminated. Trials with a reported site in the US appear to show some variation: almost half are still open or planned (155 of 306, 51%), 35% (106 of 306) are completed, and 15% (45 of 306) are terminated. Completed trials with information reported on its clinical phase (36 of 306, 12%) suggest that four of them are in Phase I, 14 in Phase II, and 18 in Phase III.

The average duration of completed trials for medical device trials for anxiety, depression and/or psychosis is 2.3 years, without significant differences across the different conditions: 2.2 years for anxiety, 2.4 years for depression, and 2.4 years for psychosis. The average duration of completed medical device trials appears to be, *a priori*, getting shorter. Completed trials that started in 2013-2018 have an average duration of 2.6 years, whereas those that started in 2018–2023 have an average duration of 2.2 years.

Figure 8 provides further insights into how the number of trials for medical devices has changed over time. The figure shows all trials, regardless of status and information on trial phase, according to their reported start year between 2013 and 2022. The number of trials for medical devices for depression started between 2013 and 2020 appears to be somewhat volatile, ranging between 20 and 40 trials starting each year. This appears to be relatively more stable for medical devices for anxiety and psychosis, with 5 to 15 clinical trials starting each year over this same period.

After this period, there appears to be a relatively sharp increase in the number of trials started for medical devices for depression. There were 43 trials for medical devices for depression that started in 2021, and 53 in 2022. Respectively, these figures are 40% and 72% larger than the 2013–2020 annual average. The changes are even more pronounced regarding the number of trials for medical devices for anxiety, where 31 and 30 trials started in 2021 and 2022, respectively, compared to an annual average of 9 trials over 2013–2020. Lastly, the same can be said about the number of trials for medical devices for psychosis, but only for 2022. To a large extent, the changes in the trends would have been driven by a growing market triggered by the COVID-19 pandemic in 2020.

Figure 8 Number of clinical trials by start year (medical devices)



Source: GlobalData, Technopolis analysis.

4.2.4 *Digital therapeutics*

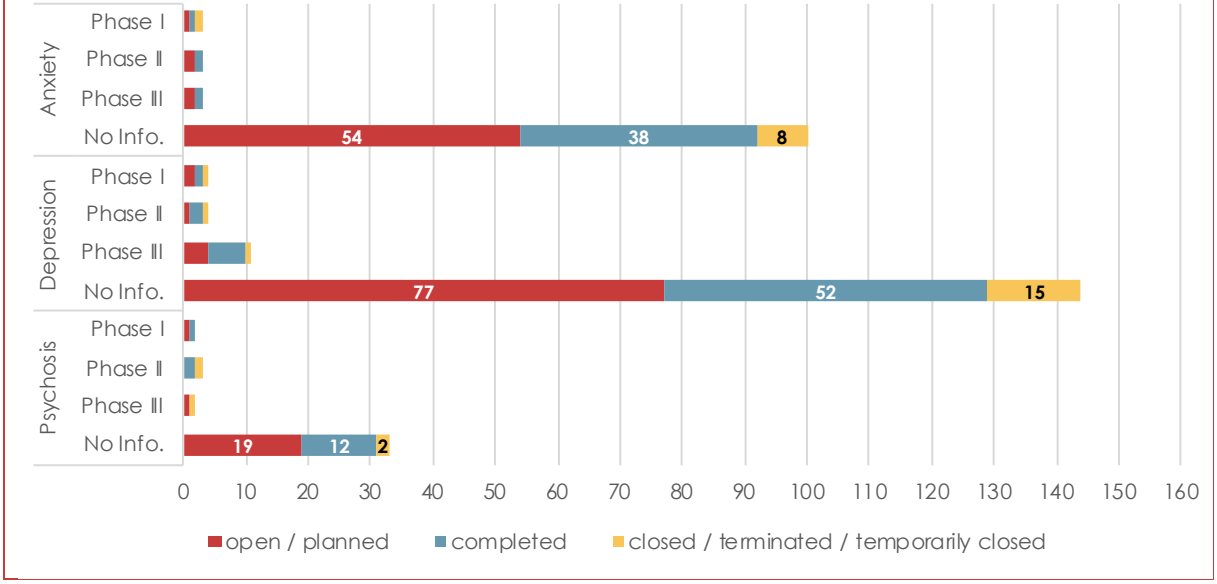
GlobalData's Clinical Trial Database also contains information on 237 trials for digital therapeutics intended to prevent, diagnose, or treat anxiety, depression and/or psychosis. In the dataset, we find 53 (22%) trials for digital therapeutics intended only for anxiety, 94 (40%) only for depression, and 19 (8%) only for psychosis. There are 50 trials (21%) that are intended for digital therapeutics used for anxiety and depression, two (1%) for anxiety and psychosis, 15 (6%) for psychosis and depression, and four (2%) where the intended use appears to be for all three conditions.

Where information is provided on the trial phase of the clinical trials, these are categorised as Phase 0, Phase I, Phase II, Phase III, Phase IV or as a combination of these (e.g. Phase I/II, Phase II/III, etc.). Most trials for digital therapeutics, however, lack this information, as well as the data needed to compute an aggregated PoS and LoA for each indication at each stage. Concretely, this is the case in 90% of trials for anxiety, 88% of trials for depression, and 83% of trials for psychosis. This is due, in great part, to the regulatory pathway to which digital therapeutics are subject, which are not always required to go through defined clinical phases. The extent of this is further depicted in Figure 9, which additionally illustrates the status of the trials. The categorisation of trial status is the same as the ones used in the analysis of non-digital medical device trials in Section 1.1.1. All in all, the figure suggests that most trials are currently open or planned, and only a small portion are closed or have been terminated.[v]

Concerning the location of trials and sites, there appears to be a greater number of trials for digital therapeutics with at least one reported site in the US (130 of 237, 55%), compared to Germany (16 of 237, 7%) and the UK (15 of 237, 6%). None of the trials in the dataset are reportedly conducting the trial in South Africa. Other reported sites include European countries (Belgium, France, Spain, among others) and countries in Asia (including China and South Korea, among others). There is a small handful of trials with reported sites in South America (Brazil, Chile) and one trial with a reported site in Uganda. There is not enough information on the trials' phases to comment on whether products being trialled in any one of these countries appear to be more advanced. It is apparent that trials for digital medical devices appears to be biased towards higher-income countries that could presumably be driven, at least in part, by a larger market for these types of interventions (e.g. a larger population with means to access these types of interventions) and a larger skilled labour pool (i.e. software developers, UX designers, etc.).

[v] In the Figure, Phase I trials include all trials reported to be in Phase 0 and Phase 1; Phase II trials include all trials reported to be in Phase I/II and Phase II; Phase III trials include all trials reported to be in Phase II/III, Phase III, Phase III/IV and Phase IV.

Figure 9 Number of digital therapeutic device trials by disorder, phase, and status (2013–2023)

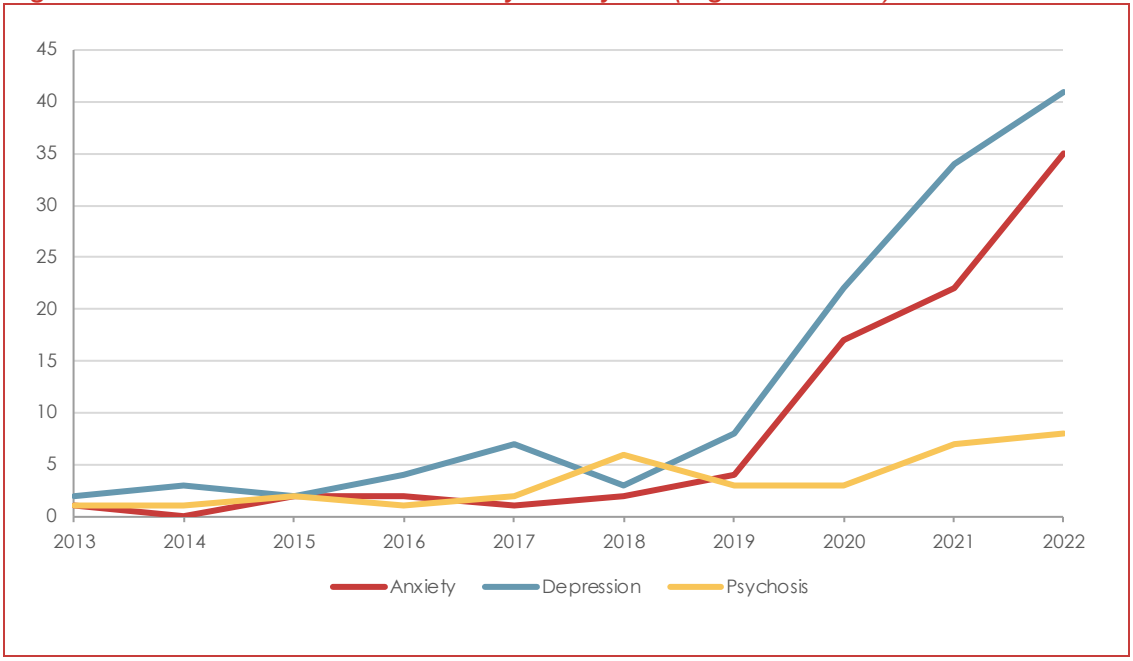


Source: GlobalData, Technopolis analysis.

The average duration of completed digital therapeutics trials is shorter than that of completed medical device trials (1.5 years vs 2.3 years). There is not much variation in the average duration across different countries, but, overall, the data suggests that trials for digital therapeutics are getting shorter over time: 2.2 years for completed trials that started between 2013 and 2018, compared to 1.4 years for trials that started between 2018 and 2023.

Considering the trials' start date, irrespective of their status and phase information, reveals that the number of trials starting every year has increased considerably since 2020. The average number of trials started between 2013 and 2019 for digital therapeutics for anxiety, depression, and psychosis was, respectively, 1.7, 4.1 and 2.3. Over the 2020–2022 period, the average number of trials started for digital therapeutics to treat these conditions jumped to 24.6 for anxiety, 32.3 for depression and 2.3 for psychosis. Once again, these changes can be, at least in some part, attributed to the onset of the COVID-19 pandemic in 2020.

Figure 10 Number of clinical trials by start year (digital devices)



Source: GlobalData, Technopolis analysis.

4.3 The market for mental health Interventions

4.3.1 Prevalence of mental health conditions

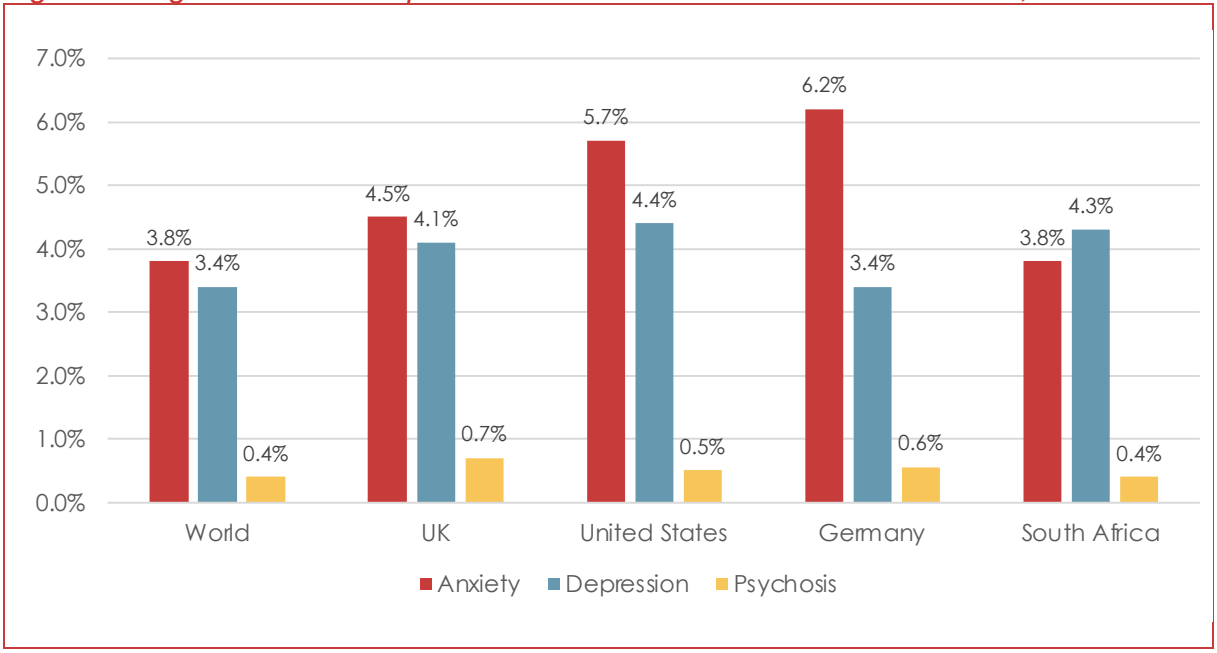
We analysed data from the Global Burden of Disease (GBD) dataset[51] to illustrate the prevalence rates of different mental health conditions globally and in four different countries. This data source employs a multidimensional approach, combining information from representative surveys, medical records, and statistical modelling. The estimates reveal the share of individuals affected by each condition in 2019, irrespective of whether they received a formal diagnosis from a healthcare professional.

In 2019, an estimated 970 million individuals, equivalent to 1 in 8 people globally, experienced a mental illness causing significant disturbance in thinking, emotional regulation, or behaviour. Prevalence rates differed across mental health conditions, with 3.8% of the global population affected by anxiety disorders, 3.4% by depression, 0.4% by psychosis (which includes an average between bipolar disorders (0.5%) and schizophrenia (0.3%) (see Figure 10). High-income countries such as the UK, the US, and Germany, reported higher prevalence rates of anxiety disorder than the global average (4.5%–6.2%, compared to 3.8% global average).

Variations in the prevalence of disorders among countries may stem from differences in the distribution of associated risk factors and cultural factors (such as stigma or willingness to seek treatment). However, differences in data availability for different conditions and regions can also affect these figures and need to

be considered when interpreting the data. For example, while mental health conditions such as depression and anxiety have more extensive global coverage, the availability of data on other conditions, such as bipolar disorder, is more limited.[57] For depression, data from North America and Western Europe encompasses a larger share of the adult population compared to data from South Africa.[52]

Figure 11 Age-standardised prevalence rates of mental health disorders, 2019T



Source: IHME, Global Burden of Disease (1990–2019) Dattani *et al.*, (2023) – 'Mental Health'. *Note: The data for psychosis is an average of bipolar disorder and schizophrenia.*

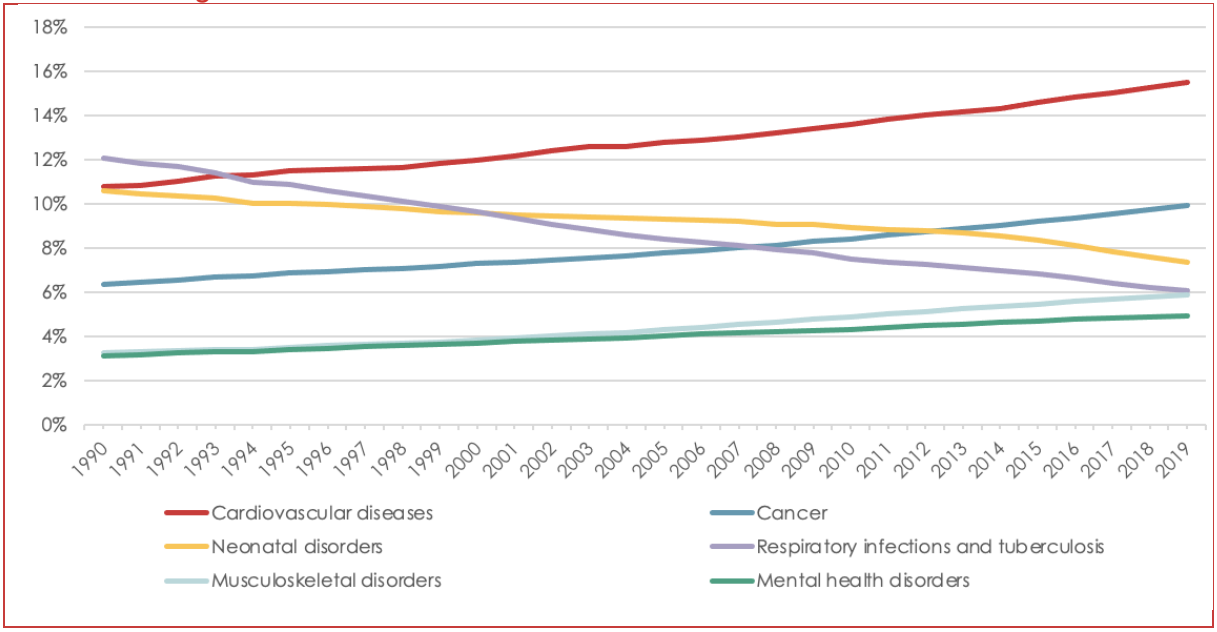
The GBD 2019 study also estimated the burden of mental health disorders around the world. The Disability-Adjusted Life Years (DALYs) metric estimates the years of healthy life lost due to premature mortality or disability, offering a measure of the impact of mental health disorders on populations.[w]

Globally, 125 million DALYs are attributed to mental health conditions, accounting for 5% of the total disease burden from all causes. Notably, mental health is the sixth largest contributor to the total disease burden, behind cardiovascular disease (16%), cancer (10%), neonatal disorders (7%), respiratory infections and tuberculosis (6%) and musculoskeletal disorders (6%). There has been a notable

[w] DALYs combines the effects of **mortality** (i.e. Years of Life Lost (YLL) due to premature death) and **morbidity** (i.e. Years Lived with Disability (YLD) due to non-fatal health condition)). The YLD is calculated by multiplying the prevalence of a health conditions at varying levels of severity by an appropriate disability weight which represents a magnitude of health loss associated with a given health condition.

decline in the global disease burden from all causes in the past three decades, falling from 2.6 billion in 1990 to 2.5 billion DALYs (around 3% reduction). However, mental health conditions have become increasingly prominent, rising from 80 million DALYs to 125 million DALYs over the same period (representing an increase from 3% to 5% of the total disease burden) (see Figure 12).

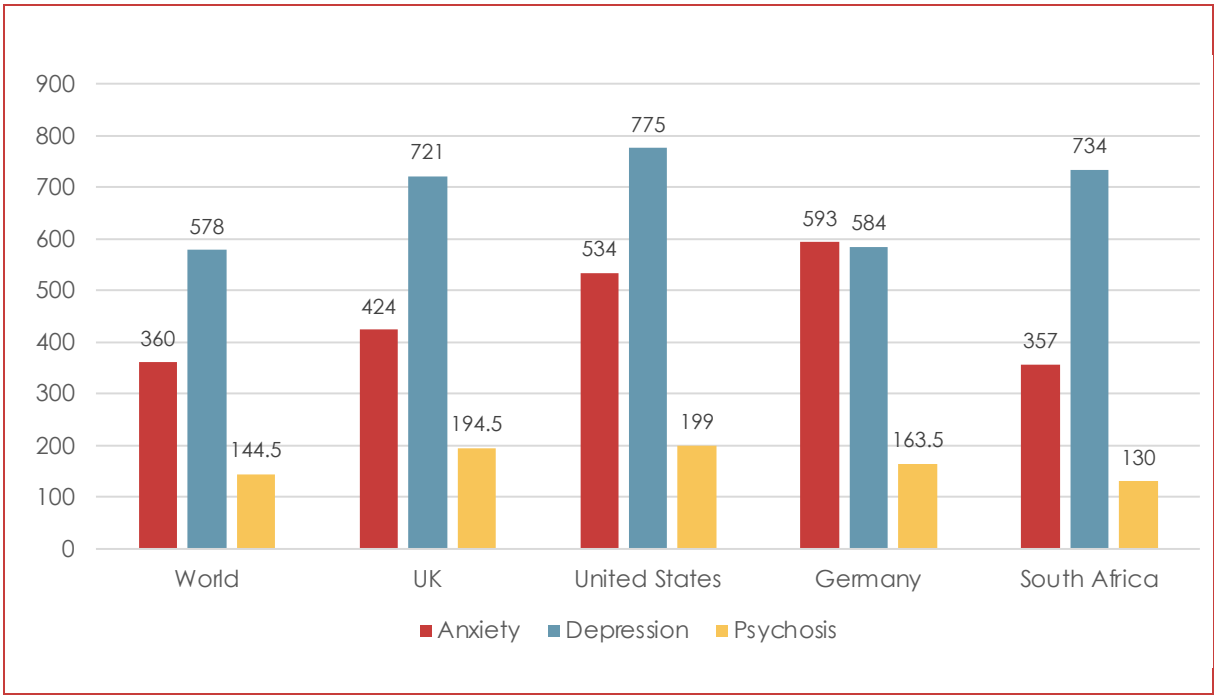
Figure 12 DALYs as a share of the total disease burden for the top six conditions with the highest burden



Source: IHME, Global Burden of Disease (1990–2019). *Note: Mental health disorders include depressive disorders, anxiety disorders, bipolar disorder, schizophrenia, autism spectrum disorders, conduct disorder, attention-deficit hyperactivity disorder, eating disorders, idiopathic developmental intellectual disability, and a residual category of other mental disorders.*

The burden of depression and anxiety is considerably higher compared to other types of mental health disorders (such as bipolar disorders and schizophrenia) (Figure 13), due in part to their higher prevalence rates (Figure 11). Despite a slightly lower global prevalence rate, depression appears to have a greater disability burden than anxiety. This discrepancy may be partly attributed to the profound impact depression has on daily function as reflected in the higher disability weights used in the DALY calculations.[53] These estimates are further influenced by the interplay between prevalence rates in age cohorts and the distribution of case severity within the population.

Figure 13 Burden of disease, 2019 (DALYs per 100,000 people), both sex and age standardised



Source: IHME, Global Burden of Disease (1990–2019), Dattani *et al.* (2023) – 'Mental Health'. *Note: The data for psychosis is an average of bipolar disorder and schizophrenia.*

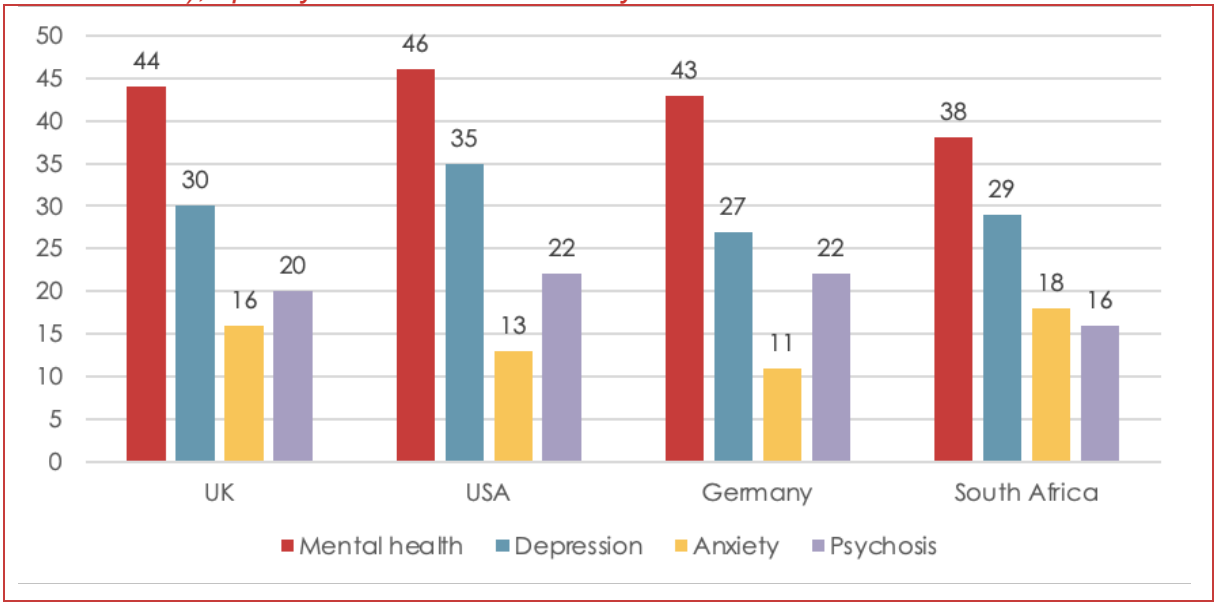
4.3.2 *Pipeline and marketed pharmaceuticals*

We used GlobalData's pipeline and marketed drug database to explore the number of pharmaceutical products across the R&D lifecycle from early development through commercialisation.[54] Each drug in the database has a mechanism of action describing the specific biochemical interactions through which the drug produces its effects in the body. These mechanisms describe the specific molecular targets, or combination of targets, to which the drug binds, such as an enzyme or receptors within the body.

To provide a deeper understanding of the therapeutic landscape for mental health conditions, we estimated the number of drugs with distinct mechanisms of action, rather than the number of pharmaceutical products available on the market (Figure 14). From the countries in our analysis, the US has the highest number of marketed drugs with distinct market mechanisms of action (46 products), followed by the UK (44 products), Germany (43 products) and South Africa (38 products). Across all four countries, depression exhibits a higher number of distinct mechanisms of action than anxiety and psychosis, indicating a relatively more diverse range of therapeutic options for addressing this specific mental health condition. In comparison, psychosis demonstrates a lower number of

market mechanisms of action, ranging from 16 distinct mechanisms in South Africa to 22 distinct mechanisms in the US. Anxiety exhibits the fewest distinct mechanisms of action, indicating comparatively more limited unique therapeutic options for the treatment of this condition.

Figure 14 Number of marketed drugs with distinct mechanisms of action (1983–2024), split by indication and country



Source: GlobalData, Technopolis analysis. *Note: The analysis counts the distinct mechanism of action at the most advanced stage of development for each indication/country combination and removes the duplicates. One mechanism of action can be effective in treating two or more mental health indications and, as such, the sum of the three conditions is higher than the count for mental health overall.*

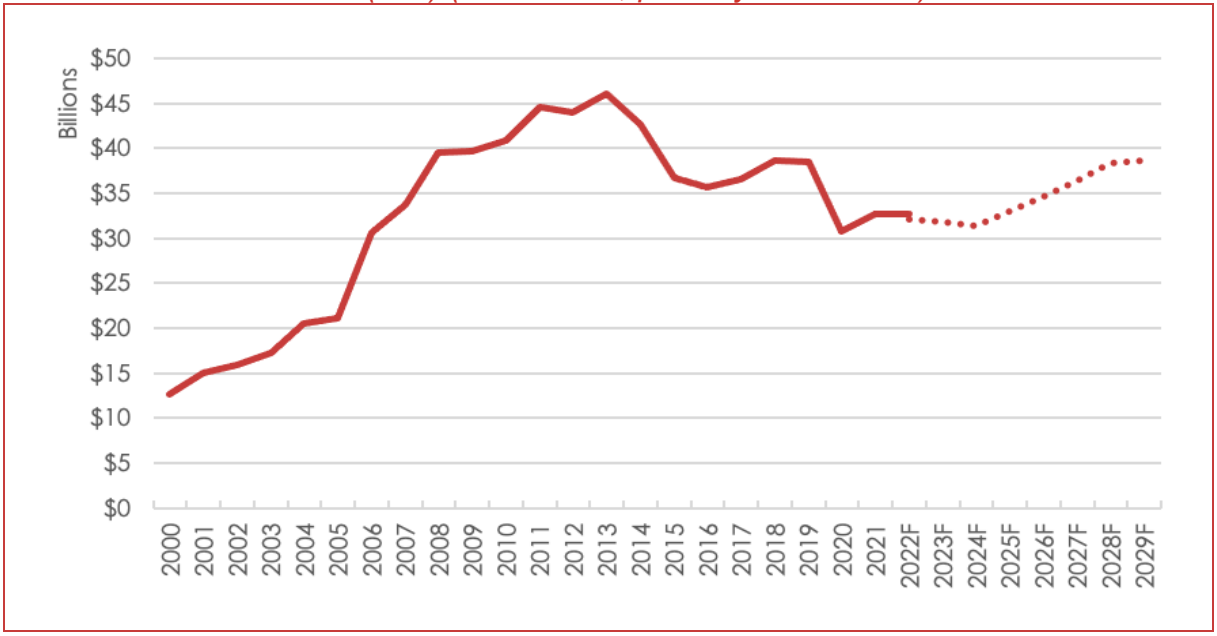
We used GlobalData's Drugs by Manufacturing database to estimate the market size of pharmaceutical drugs used for the treatment of mental health conditions.[55] The market size is defined as the aggregate sales revenue generated by manufacturers, based on the retail price of each drug. The database covers innovator and biosimilar drugs approved by the EMA centralised pathway, UK MHRA, and the US FDA.

Figure 15 shows that the market size for mental health pharmaceutical interventions reached approximately $32bn in 2021, reflecting the aggregate sales revenue generated by 135 drugs. There was a consistent annual increase in the market size from 2000 to 2013, followed by a subsequent decline in the ensuing years. However, based on analyst and patient-based projections, the market is expected to grow to $39bn (18% increase) by 2029. This projected growth is equivalent to an annual average growth rate of 2%.

Table 12 provides examples of top-grossing pharmaceutical products marketed in different territories around

the world for the treatment of different mental health conditions. As Globaldata is incomplete, it is important to acknowledge that there may be other pharmaceutical products with higher revenue for which we do not have sales data. The list is intended to serve as an illustrative reference, providing examples of products that have generated relatively higher revenue sales compared to other similar products with available sales data.

Figure 15 Sales revenue generated from pipeline and marketed drugs for mental health conditions ($bn) (2000–2021, plus 8-year forecast)



Source: GlobalData, *Note: The dataset integrates information from prescription drug sales with company financials sourced from regulatory authorities and published company annual financial reports. The data represents total sales from all geographies for a drug where the company is marketing, and as such, cannot be broken down by individual regions. The forecasts are based on analyst consensus forecasts and patient-based forecasts derived from disease analyst reports.*

Table 12 Examples of the top grossing pharmaceutical products for the treatment of mental health indications

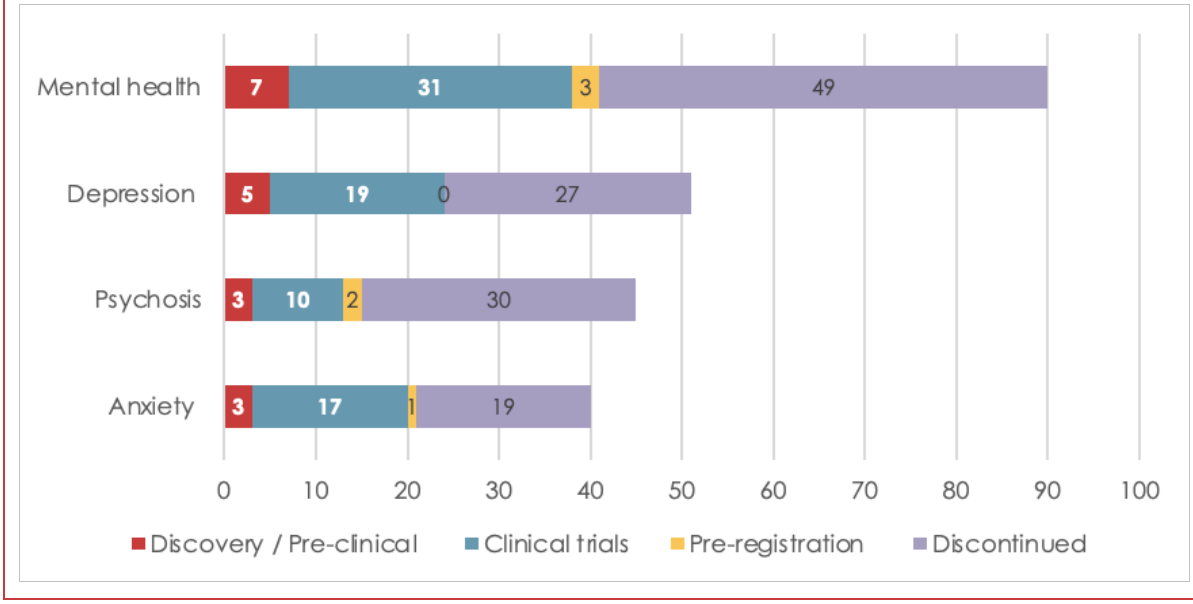
Drug name	Condition(s)	Territory where drug is marketed	Drug type
Paliperidone palmitate LA	Schizophrenia	7 EU countries, UK, Switzerland, Russia, USA, Canada, Australia, New Zealand, India, Indonesia, China, Japan, South Korea, Mexico, Brazil, South Africa, Israel	Innovator (Non- New Molecular Entity, NME)
Lurasidone hydrochloride	Schizophrenia, Bipolar disorder	EU countries, UK, Switzerland, Russia, USA, Canada, Australia, Indonesia, China, Japan, South Korea, Brazil	Innovator (New Molecular Entity, NME)
Cariprazine	Schizophrenia, Bipolar disorder	EU countries, UK, Switzerland, Russia, USA, Canada, Australia, Indonesia, South Africa	Innovator (New Molecular Entity, NME)
Brexpiprazole	Major Depressive Disorder, Schizophrenia	EU countries, UK, Switzerland, USA, Canada, Australia, Indonesia, Japan, South Korea, Brazil, Mexico, South Africa, Israel	Innovator (New Molecular Entity, NME)
Vortioxetine hydrobromide	Major Depressive Disorder	EU countries, UK, Switzerland, Russia, USA, Canada, Australia, New Zealand, India, Indonesia, China, Japan, South Korea, Mexico, Brazil, South Africa, Israel	Innovator (New Molecular Entity, NME)
Lyrica	Generalised Anxiety Disorder	EU countries, UK, Switzerland, Russia, USA, Canada, Australia, India, Indonesia, China, Mexico	Innovator (New Molecular Entity, NME)

Drug name	Condition(s)	Territory where drug is marketed	Drug type
Duloxetine hydrochloride DR	Generalised Anxiety Disorder, Major Depressive Disorder	EU, UK, Switzerland, Russia, USA, Canada, Australia, Indonesia, China, Japan, South Korea, Mexico, Brazil, South Africa, Israel	Innovator (New Molecular Entity, NME)
Effexor XR	Major Depressive Disorder; Panic Disorders, Generalized Anxiety Disorder (GAD), Social Anxiety Disorder	6 EU countries, UK, Switzerland, USA, Canada, Australia, New Zealand, India, Indonesia, China, Japan, South Korea, Mexico, Brazil, South Africa, Israel	Innovator (Non- New Molecular Entity, NME)
Zoloft	Major Depressive Disorder; Obsessive-Compulsive Disorder; Panic Disorders; Post-Traumatic Stress Disorder (PTSD); Social Anxiety Disorder	4 EU countries, Switzerland, Russia, USA, Canada, Australia, Indonesia, China, Japan, South Korea, Brazil, South Africa	Innovator (New Molecular Entity, NME)

Source: GlobalData,

According to GlobalData, there are 90 pipeline drugs with distinct mechanisms of action in the US, of which 7 candidates (8%) are in the pre-clinical phases, 31 (34%) have entered clinical trials, 3 (3%) are in the process of pre-registration, and 49 (54%) are discontinued (Figure 16).

Figure 16 Number of pipeline drugs with distinct mechanisms of action in the US (2000–2024), split by indication



Source: GlobalData, Technopolis analysis. *Note: The analysis counts the distinct mechanism of action at the most advanced stage of development for each indication/country combination and removes the duplicates. One mechanism of action can be effective in treating two or more mental health indications and, as such, the sum of the three conditions is higher than the count for mental health overall.*

4.3.3 *Pipeline and marketed devices (non-digital)*

We used GlobalData's pipeline and marketed products database to estimate the number of non-digital medical devices across the R&D lifecycle from early development through commercialisation.[56,57] The database collates information from various sources, including regulatory bodies, company websites, conference presentations, and clinical trial registers.

According to the data, 158 non-digital medical devices have been approved since 2010 for the diagnosis, management, and treatment of different mental health conditions. Notably, around two-thirds of these devices (100 devices) are approved in the US, with a comparatively lower number of approvals in the UK (21 products), Germany (13 products), and South Africa (1 product). Around 55% of products with documented approval or market launch dates (62 out of 113 products) have secured their approval in 2018 or after. Table 14 provides examples of the top three non-digital medical devices with most approvals around the world for each of the three conditions (anxiety, depression, and psychosis).

There are 351 non-digital medical device for mental health conditions that are currently at various stages of development. Of them, 160 products are progressing through the pre-clinical and clinical trial phases, ten products are in the process of approval, and 181 products are discontinued or inactive.

Most of the pipeline candidates that are not discontinued/inactive are aimed at treating depression (84 products) and anxiety (80 products), and slightly fewer candidates are aimed at psychosis (30 products). Close to two-thirds of pipeline digital products that are not discontinued/inactive are expected to enter the US market post approval (104 products), compared to only one pipeline product potentially entering the UK market and zero pipeline candidates entering the German or South African markets.

Table 13 Number of approved medical devices (non-digital) (2010–2024), split by indication and country

	Anxiety	Depression	Psychosis	Mental health*
UK	13	12	1	21
US	56	60	13	100
Germany	8	8	0	13
South Africa	0	1	0	1
Global**	**82**	**89**	**27**	**158**

Source: GlobalData, Technopolis analysis. *Note: *One medical device may be used for more than one mental health condition. **The database covers 32 countries.*

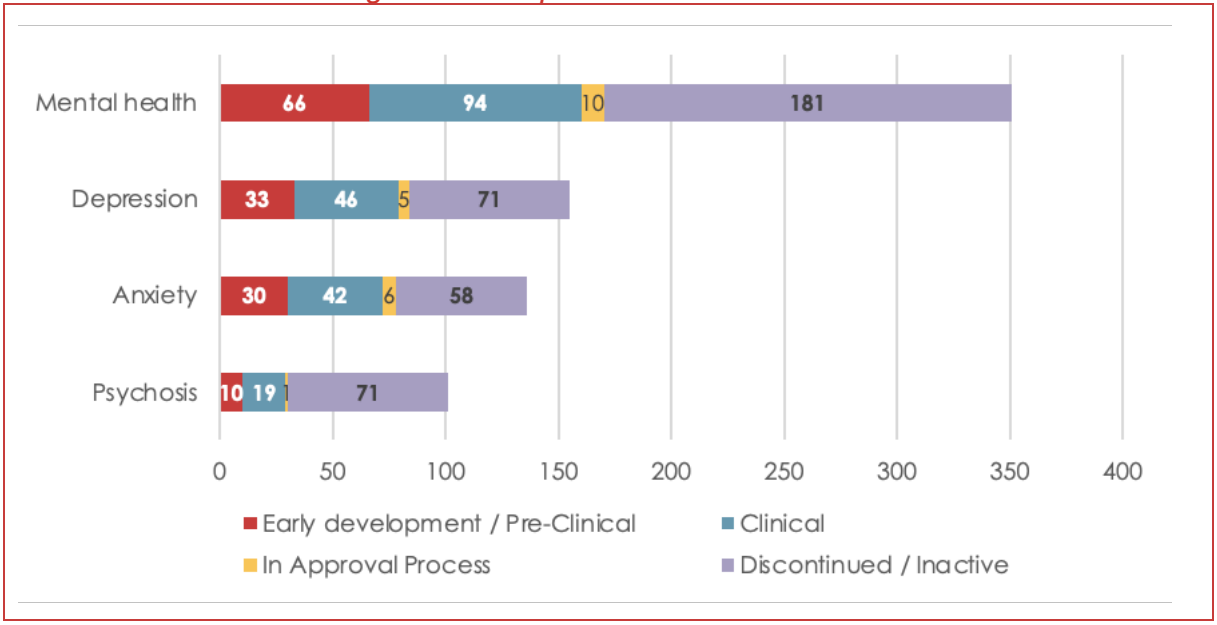
Table 14 Examples of medical devices (non-digital) with approval in the US

Name	Description	Approved indication	Date first approved *	Number of countries with approval
Activa PC Neurostimulator	Delivers a controlled electrical pulse to the internal globus pallidus or the subthalamic nucleus	Obsessive-Compulsive Disorder	2009	26
NeuroStar Advanced Therapy System	A non-invasive computerised electromechanical medical device intended for transcranial magnetic stimulation. It is designed to deliver non-invasive magnetic fields to induce electrical currents targeting specific regions of the cerebral cortex	Obsessive-Compulsive Disorder, Major Depressive Disorder	2020	26
VNS Therapy System	An implantable device intended for vagus nerve stimulation (VNS). It is designed to deliver mild pulses to the vagus nerve from the pulse generator at regular intervals throughout the day to stop seizures	Treatment Resistant Depression	1997	25
SmartGoggles	SmartGoggles is intended for stress management, sleep management, and anxiety management. It is designed to facilitate lower heart rate, reduce stress, and anxiety, and optimise sleep	Anxiety Disorders, Stress		23
HDCKit System	A non-invasive transcranial electrical stimulation system intended for transcranial direct current stimulation (tDCS). It is designed to deliver weak electrical current through two scalp electrodes by a portable battery-powered stimulator to reduce symptoms related to chronic pain and depression	Depression	2009	10
Nurostym tES system	Nurostym tES system is intended for transcranial electrical stimulation. It is designed to aid in non-invasive stimulation of the central nervous system using low direct current	Schizophrenia, Depression	2021	10
Magstim Super Rapid 2 – Repetitive Transcranial Magnetic Stimulator	A computerised, electromechanical single pulse and repetitive stimulator intended for repetitive transcranial magnetic stimulation. It is designed to deliver electrical currents to stimulate the peripheral nerves by using electrodes	Major Depressive Disorder	2005	9
MyCare Psychiatry	A rapid, point of care test intended for therapeutic drug monitoring. It is	Schizophrenia	2018	3

Name	Description	Approved indication	Date first approved *	Number of countries with approval
Clozapine Assay Kit	designed to measure clozapine drug levels in a patient's blood sample. It aids physicians to personalise patient dosing for optimal efficacy			
Athelas One Point-Of-Care Device	An automated cell counter system, neutrophil monitoring device intended for haematology testing. It is designed to monitor neutrophils, lymphocytes, platelets, WBCS, morphology, and cell activation in patient's finger prick blood sample. It consists of Athelas One analyser and the Athelas One Test Strips. Its test strip collects a blood sample to generate a layer of cells for counting and image analysis	Schizophrenia	2018	2

Source: GlobalData, Technopolis analysis. *Note: *the dataset is incomplete as some devices are missing approval dates in certain geographies.*

Figure 17 Number of pipeline non-digital medical devices (2007–2024), split by indication and stage of development



Source: GlobalData, Technopolis analysis. *Note: One medical device may be associated with more than one mental health condition; the total number for mental health includes unique devices only.*

Table 15 Number of pipeline non-digital medical devices (excluding discontinued/inactive products) (2007–2024), split by indication and country

	Anxiety	Depression	Psychosis	Mental health
UK	1	1	0	1
USA	50	53	17	104
Germany	0	0	0	0
South Africa	0	0	0	0
Global	**80**	**84**	**30**	**170**

Source: GlobalData, Technopolis analysis. *Note: One medical device may be associated with more than one mental health condition; the total number for mental health includes unique devices only.*

4.3.4 Digital therapeutics

According to the GlobalData data, 115 digital therapeutics are approved globally for the diagnosis, management, and treatment of different mental health conditions. Of those, 58% (67 products) are approved in the US and significantly fewer products are approved in the UK (19 products, 17%) or Germany (11 products, 10%). Globally and across the four countries in our analysis, most digital therapeutics are marketed for anxiety and/or depression, while significantly fewer products are marketed for psychosis conditions. Among the analysed digital devices, 50 out of 115 devices have documented approval or market launch dates, with a significant majority (72%) securing approval in the past five years alone. Table 17 presents examples of the top three digital medical devices with the most approvals around the world for each of the three conditions (anxiety, depression, and psychosis). This list includes digital devices recorded in the GlobalData database.

Table 16 Number of marketed digital therapeutics (2010–2024), split by indication and country

	Anxiety	Depression	Psychosis	Mental health *
UK	15	6	0	19
USA	52	36	4	67
Germany	9	5	0	11
South Africa	0	0	0	0
Global**	**91**	**57**	**8**	**115**

Source: GlobalData. *Note: *One digital therapeutic device may be associated with more than one mental health condition; the total number for mental health includes unique therapeutics only. **The database covers 32 countries.*

Table 17 Examples of digital therapeutics with FDA approval or EUA designation

Name	Description	Approved indication	Date approved	Number of countries with approval
Xen – Vagus Nerve Stimulation Device	A pocket-sized wearable device intended for vagus nerve stimulation. It is designed to apply electrical stimulation to the vagus nerve in the ear through the Xen headphones. The Neuvana app allows users to customise and control their Xen sessions via Bluetooth connection	Anxiety disorder, stress		20
Deprexis	A digital therapy consisting of recognised treatment elements from cognitive behavioural therapy	Depression	2020	9
Oncomfort Sedakit	A digital sedation software as medical device (SAMD) and virtual reality solution intended for digital therapeutics. It is designed to reduce pain and anxiety in patients without medication. It features 3D virtual sessions with hypnotherapeutic scripts and immersive sounds, dissociating patients from their pain and anxiety	Anxiety disorder		8

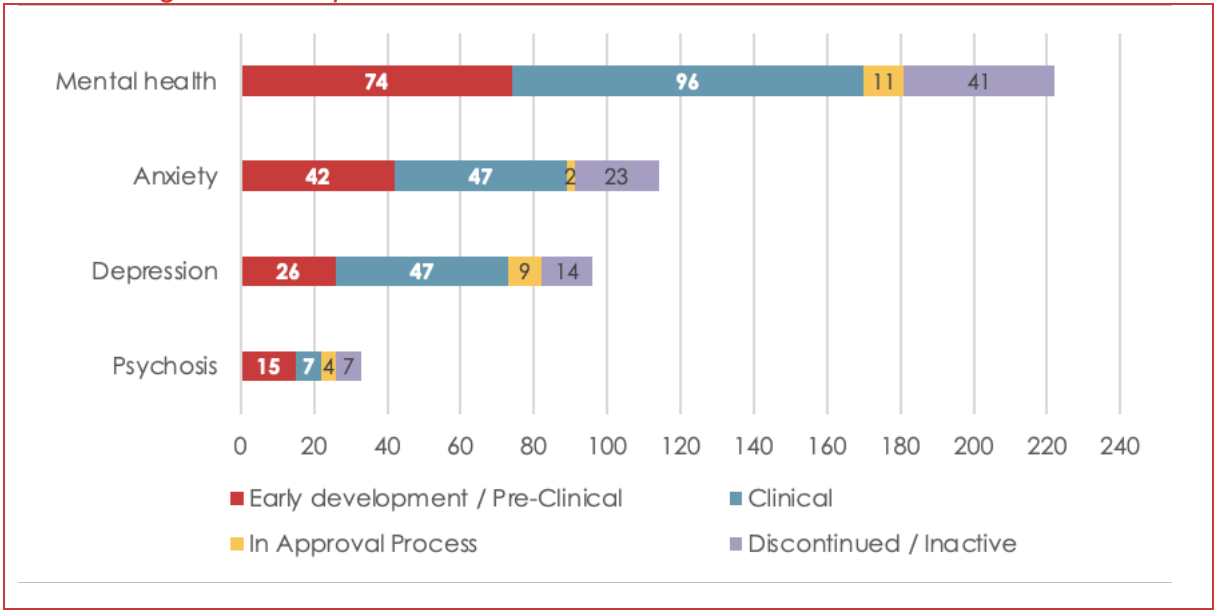
Name	Description	Approved indication	Date approved	Number of countries with approval
C2Companion Software	A digital therapeutic application intended for virtual reality exposure therapy. It is designed to stimulate cognitive functions, body mobility and improve the semantic and procedural memory properties of the patient. It allows the users to play and care in a stimulating environment to perform multiple tasks that activate positive memories related to the type of experience, maximising the hedonic potential	Anxiety disorder, Depression		5
Neural Navigator	A software intended to be used during transcranial magnetic stimulation (TMS). It is designed to perform image guided stereotaxy and target brain areas indicated on an MRI scan with a precision of 4 mm or better. It can load and visualise individual MRI scans, tissue maps (e.g. grey matter), fMRI activation maps and cardiotropic facial markers	Depression	2016	5
Starstim 32	A wearable and wireless 32-channel tES stimulator intended for Electro-encephalagraphy (EEG) monitoring. It is designed to stimulate the transcranial system and record tiny electrical impulses generated by the neurons in the brain. It is based on Wearable Technology. The device integrates advanced digital technology to deliver precise multi-channel neurostimulation and simultaneously record and analyse EEG data. It features digital control for personalised brain targeting, wireless data transmission, and software-driven customisation	Depression	2014	5
MINDD STIM	A portable, wearable transcranial direct current stimulation (tDCS) headband	Schizophrenia, PTSD	2017	2

Name	Description	Approved indication	Date approved	Number of countries with approval
	intended for the treatment of neuropsychiatric disorders. It is designed to deliver weak electric current to the unbalanced dorsolateral prefrontal cortex (DLPFC) hub of the cognitive and emotional process in our brain. The device is integrated into a telemedicine platform which collects and analysis information through the entire treatment process. Patients can record and monitor their symptoms directly on the platform using a mobile device			
QyScore Software	A cloud-based software intended for neuroimaging. It is designed to automatically provides segmentations and measures of brain structures and lesions from a set of MR images for patients between the ages of 20 and 90	Schizophrenia	2017	2
Abilify MyCite	A drug-device combination digital medicine intended for drug response measurement. It is designed to measure actual medication-taking patterns and physiologic response of the drug. It is a combination of a drug ABILIFY (aripiprazole) and proteus ingestible sensor that is embedded in a single tablet. Its sensor sends the signal to the wearable Proteus patch after reaching the stomach and it records, collects and time-stamps the information from the ingestible sensor including patient metrics, rest, body angle and activity patterns. The Proteus patch transmits the information to a mobile application so that patients can track the ingestion of the medications on their smartphone	Schizophrenia, Bipolar disorder, depression	2017	2

Source: Globaldata. *Note: *the dataset is incomplete as some devices are missing approval dates in certain geographies.*

Analysis of GlobalData indicates that 222 digital therapeutics are in the pipeline, of which 74 products (33%) are in the early-development or pre-clinical stages and 96 products (43%) have entered clinical trials. Further 11 digital therapeutics (5%) are currently in the approval process, but the remaining 41 products (18%) are discontinued or inactive. As shown in Table 18, around 62% of all pipeline digital products that are still active (113 out of 181) are expected to be commercialised in the US, with significantly fewer products expected to enter the UK or German markets. Most pipeline digital therapeutics that are still active are for anxiety (91 products) or depression (82 products). Notably, there are 26 pipeline digital therapeutics for psychosis that are still in active development, representing a significant increase compared to the current market landscape for the treatment of this condition.

Figure 18 Number of pipeline digital therapeutics (2007–2024), split by indication and stage of development



Source: Globaldata, Technopolis analysis. *Note: One digital therapeutic device may be associated with more than one mental health condition; the total number for mental health includes unique therapeutics only.*

Table 18 Number of pipeline digital therapeutics (excluding discontinued/inactive products) (2007–2024), split by indication and country

	Anxiety	Depression	Psychosis	Total
UK	3	3	1	6
US	61	47	20	113
Germany	0	1	0	1
South Africa	0	0	0	0
Global	**91**	**82**	**26**	**181**

Source: Globaldata, Technopolis analysis. *Note: One digital therapeutic device may be associated with more than one mental health condition; the total number for mental health includes unique therapeutics only.*

4.3.5 Unmet need for mental health interventions

Many people dealing with mental health disorders fail to receive a formal diagnosis from a medical professional or face challenges in accessing any form of treatment or minimally adequate treatment (MAT) for their condition.[58,59]

A survey of the prevalence and social cost of mental health disorders in 21 countries indicated that around two-thirds of individuals (64%) in high-income countries who met the criteria for anxiety disorders did not receive treatment for their condition.[60] The treatment gap for anxiety was even larger in upper-middle-income countries (80%) and lower-middle-income countries (87%). Similarly, a systematic review of the literature based on data from 84 countries between 2000 and 2021, indicated that the treatment gap for Major Depressive Disorder (MDD) was considerable in many parts of the world. The study found that the treatment coverage for mental health services use ranged from 33% in high-income countries to as low as 8% in low and middle-income countries.[61]

Furthermore, research has indicated that even upon receiving adequate medical attention, a significant proportion may not respond to conventional treatment approaches.[62] From 8.9 million patients diagnosed with MDD in the US, around 31% (2.8 million patients) had Treatment-Resistant Depression (TRD) because they failed to respond adequately to conventional treatment.[x]

4.3.6 Barriers to patient/user access

The potential market size for treatments is strongly influenced by the existing prevalence rates of health conditions and their anticipated growth

[x] The FDA and EMA define Treatment Resistant Depression (TRD) as failure to adequately respond to a minimum of two antidepressant regimens, despite adequate treatment dose, duration and adherence.

trajectories. However, several other factors are also at play. For example, factors that contribute to the treatment gap in LMICs, and thus limit the size of the market, include the need for more healthcare professionals to increase access to mental health treatments and financial challenges related to the affordability of treatment. A growing body of evidence is bringing attention to populations in LMICs – and also in high-income countries – who experience exclusion from mainstream society. The data shows that people experiencing homelessness, imprisonment, drug addiction and extreme poverty are more likely to suffer from mental health problems and are less likely to receive treatment.[63–66]

5 Involvement of People with Lived Experience – perspectives and priorities

Involvement of People with Lived Experience (PWLE) throughout the research process, e.g. in study design, participant recruitment, and data collection, has shown to be beneficial in ensuring that research is relevant to and inclusive of the perspectives and needs of those affected.[67] PWLE's first-hand insights into the complexities of mental health conditions can hence shape the research process to enhance the authenticity and depth of research findings. PWLE can also provide guidance to ensure research is conducted ethically and findings disseminated in broadly accessible formats and can serve as advocates for the translation of research outcomes into policies and practices that positively impact mental health services. Ultimately, the multifaceted engagement of PWLE in mental health R&D can contribute to more impactful research outcomes. This was demonstrated in our case study on gameChange, using virtual reality (VR) therapy to support people with psychosis (see Appendix G).

'We had some impact around the actual instruments used to measure health-related quality of life that were used in the study, which makes me quite proud, because we don't usually change or develop measures as a result of wishes of people with lived experience' said a lived experience expert for gameChange

For example, multiple studies have identified that a lack of co-production between developers and PWLE contributes to low engagement and uptake of mental health digital therapeutics.[68–72]

A scoping review of evidence and implementation gaps in PWLE engagement in mental health and substance use research identified several challenges in current practices. These include challenges in conceptualising PWLE engagement, developing resources, conducting research with diverse PWLE groups, and evaluating the impacts of PWLE engagement.[67] The findings highlight the need for further research to inform the development of best practice and guidelines on PWLE involvement in the mental health R&D process.

Several developers of mental health interventions consulted in this study reported involving PWLE in their R&D process for mental health interventions. The main reasons given for doing so included ensuring that interventions under development are relevant and acceptable to end users, understanding potential barriers that may hinder participation in studies, and informing the selection of real-world outcome endpoints so they are meaningful to people living with mental health conditions (e.g. being able to start a relationship, to engage more with sports, or to enter/maintain employment). Developers also reported engaging with 'third sector' organisations such as mental health

charities and NGOs, clinicians, and carers to gain insights on the needs of PWLE to inform the development of mental health interventions. Methods developers used to engage with end users included surveys, interviews, focus groups and advisory boards/panels.

The methods used to involve PWLE in research are usually not formally reported. However, there are exceptions as in the case of gameChange where peer research methods, a participatory research method in which PWLE take part in directing and conducting the research, were incorporated into the development process.[73]

Some developers highlighted challenges in engaging PWLE. These include:

- Difficulties identifying and engaging with PWLE
- Lack of knowledge of the most effective methods to meaningfully involve PWLE in the R&D process. In the UK, the NIHR Centre of Engagement and Dissemination (formally known as INVOLVE) has developed best practice guidance for PWLE involvement. However, this guidance is not specific to mental health research[74]
- The cost of PWLE involvement, which can include covering travel costs and costs to pay for childcare or care
- Some reluctance from PWLE to engage in research because of scepticism or mistrust due to past experience and feelings of power imbalance
- Possible concerns from developers around confidentiality and commercially sensitive information. Another concern has been if some national guidance (such as the Association of the British Pharmaceutical Industry (ABPI), https://www.abpi.org.uk/reputation/abpi-2021-code-of-practice) makes direct contact with PWLE difficult in some circumstances

'Incentives play a big role because we are asking people [with lived experience of mental health] time and effort to be a part of a study', said a developer.

In three of the case studies developed as part of this report, PWLE were closely involved in the product development process (see Appendix G, Appendix J, and Appendix K). The perspectives of PWLE were captured in four of the case studies and share several commonalities from the lived experience perspectives. PWLE were either directly involved in the R&D process (in some cases the developers themselves are also lived experience experts) or as end users:

- **Insights into real-life challenges:** PWLE provided first-hand insights into the daily challenges and struggles faced by individuals with mental health conditions. This helped developers and researchers gain a deeper understanding of the lived experiences of their target

audience. Additionally, it helped developers understand user priorities, preferences, and how PWLE would want to use interventions once they are developed.

- **Influence on product design:** In some cases, PWLE have contributed to the design and development process, shaping various aspects of the products. For example, in the development of digital interventions, this includes PWLE's views on aspects such as character design, scenario relevance, and avatar characteristics. This input ensured that the final products resonated with the real-life experiences of the end users. In one of the case studies, the involvement was planned for upcoming stages of the intervention testing, where developers intended to closely engage PWLE in refining the design of the device to optimise the sensations induced by the digital pill, an implantable medical device for the treatment of depression.
- **Feedback for improvement:** PWLE played a crucial role in identifying areas for improvement. For example, for digital interventions, PWLE feedback during product testing helps to refine the programmes, addressing bugs, inconsistencies, and ensuring an appropriate balance of challenge in virtual scenarios. This iterative feedback loop contributed to the overall quality of the interventions.
- **Enhancing inclusivity and contribute to accessibility considerations:** PWLE involvement not only enhanced inclusivity by accommodating participants' needs and advocating for more inclusive representations but also contributed to accessibility considerations, recognising and addressing challenges participants may face, such as difficulties leaving their homes, by allowing therapy sessions at home and covering transportation expenses.
- **Impact on outcome measures:** PWLE influence the selection of outcomes measures, ensuring their alignment with the experiences of the target population and reflect end users' priorities and perspectives on their health-related quality of life.
- **Addressing technological limitations:** In some cases, PWLE collaborated with developers in the context of technological limitations. For example, the discussion about the avatar's lack of diversity highlights how PWLE understood and worked within constraints, contributing valuable perspectives on what is feasible.
- **Better understanding of how participants experience interventions:** PWLE actively contributed to the understanding of how interventions are used and valued by end users. Their understanding stems from personal encounters with similar interventions, enabling them to empathise with end users' experiences and provide nuanced perspectives that enrich research findings. For example, in the gameChange study, researchers with lived experience undertook

research roles and conducted interviews with study participants.

Interviewees noted that collaboration with PWLE greatly enriches studies. Their contributions extend beyond design elements to influencing scenario selection, outcome measures, and overall study considerations, demonstrating the broader positive impact of lived experience involvement.

The interviewees from the case studies also highlighted that the involvement of lived experience experts in the development of interventions is sometimes not explicitly documented, such as in research publications, making it unclear if PWLE were involved.

'I would highly recommend deprexis®… it can help those who do not seek help due to stigma … it would be good to have the opportunity to say what should be changed and help with the development process …', said an end user of deprexis®

Box 1 *Involvement of PWLE from the gameChange case study (see Appendix G for the full case study)*

gameChange

Device (digital therapeutic): a simulation intervention providing practice scenarios for people with depression.

How and when were PWLE involved in the development of gameChange?

- PWLE of mental health conditions provided input to every stage of the R&D process. This included:
  - developing the study protocol and selecting and designing both the virtual reality scenarios and the characters
  - the selection and design of outcome measures for the study
  - reviewing all patient-facing materials
- The developers engaged with PWLE in workshops and advisory group meetings
- PWLE were engaged as researchers on the study
- PWLEs received compensation for their involvement. This included reimbursement of travel and other expenses, and the offer of a small financial reward.

What was the impact of PWLE involvement?

The developers reported the collaboration with PWLE greatly enriched the study, influencing multiple aspects from scenario selection to outcome measures and accessibility considerations. This was **instrumental** in ensuring the success of the study. Without PWLE the virtual reality intervention itself could not have been successfully designed and tested.

One of our lived experience experts recently published a commentary piece on the Lancet Psychiatry Commission on Transforming mental health implementation research, highlighting gaps in translating research into practice, especially in low- and middle-income countries (LMICs), emphasising the importance of considering socio-cultural factors in

mental health interventions. Shifting towards a transdisciplinary approach, as advocated by the Commission, promises better alignment with community needs and reduced stigma. The Commission's recommendation for organisational accountability and meaningful involvement of lived experience representatives offer a path to more relevant, effective, and impactful mental health interventions. By embracing these recommendations, stakeholders can improve implementation science and mental health outcomes globally.[75]

5.1 Involvement of PWLE in this study

Throughout this study, we have actively engaged our lived experience expert advisors (Claudia Sartor, Dr Nicholas Prior, and Dr Thomas Kabir) to ensure their invaluable perspectives are integrated into our research. From the early stages, we sought their guidance on stakeholder mapping to ensure inclusivity of all stakeholder groups and geographical locations. In addition, their first-hand knowledge on mental health conditions guided us in identifying barriers that may have been overlooked and to develop practical solutions that resonate with the experiences of PWLE. We also consulted them when designing surveys specifically tailored for PWLE, ensuring that the questions were sensitive, relevant, and reflective of their needs and challenges.

Our expert advisors played a crucial role in validating our approach to including PWLE perspectives throughout the research process. We regularly checked in with them to ensure that our methods and analyses accurately captured the diverse experiences and voices within the community.

Their guidance extended beyond the desk research phase; they also provided valuable insights on how best to engage with PWLE in workshops and interviews. By incorporating their recommendations, we fostered a collaborative and respectful environment that encouraged meaningful participation and input from all stakeholders.

Our lived experience expert advisors have provided us with their reflection on the study and how we can further improve future studies to ensure best practices in engaging with PWLE throughout the study process, from design to finalising the report:

'I enjoyed my time working on the project. The staff at Technopolis were very supportive and easy to work with. I found it very worthwhile looking at digital interventions across the different areas of mental health. One of my key reflections is the pace at which the field is advancing. Just a few years ago when we were developing the gameChange virtual reality program the headsets were large, cumbersome, and awkward to use. The headsets that we have now are lightweight and much cheaper. I do think that this report will need to be recommissioned or updated very regularly. I would have thought within the next two years at least. I expect that advances in artificial intelligence will also bring rapid changes. My involvement began partway through the project. I think things would have been a bit better if I

had been involved with the project from the beginning. It is at these early stages that input from people with lived experience can be particularly influential.

Another reflection is that it would have been good to have more people with lived experience from a low- or middle-income country to work with. I was fortunate enough to meet some researchers from low- or middle-income countries recently at a meeting in the USA. It was enlightening! The challenges that they face are quite different than in a western country such as the UK.

Another personal challenge was how to introduce some nuance into some of the text in this report from a lived experience perspective. For example, I don't think it's quite clear yet if purely digital interventions always work as well as blended interventions (or ones that at least have some level of in-person contact). In addition to this, there may be differences depending on your age. I would always recommend including some qualitative work when researching a digital intervention. Such work often helps answer these kinds of questions. I was involved in qualitative work for the gameChange study – which meant that it could be used in this report. But such work is unfortunately the exception rather than the rule in digital mental health.

My experience is that younger people who are more familiar with things such as smartphones are more comfortable with digital interventions – but that is a generalisation. My point is that I believe that there is a lot that we don't yet know. But also, that the field of digital health is rapidly evolving. This brings me back to my point about the need to update this report in the near future' said Dr Thomas Kabir, A lived experience expert, Senior researcher at the University of Oxford, and patient lead for gameChange.

'It was great to be part of a complex research project, and throughout all phases of the project, and I felt appreciated for my experiential knowledge. However, as a person with lived experience, having moderate experience in science and research, I still found it difficult to keep up with scientific and research jargon and I would have liked to have received more explanation or guidance on the research and scientific terms and approaches used throughout the process. Similarly, I saw the need for more exploration of how to engage people with lived experience in research (already noted in the report as a gap). Undoubtedly, there is recognition and value attached to the importance of including lived experience expertise in service delivery, but I believe that non-lived experience professionals ought to take more time in planning and learning how to include them accordingly, in a manner that promotes meaningful and authentic participation. Perhaps having a training session with peer led organisations such as the Global Mental Health Peer Network, before the project starts, would have been beneficial. GMHPN has written guidelines and policies, available to the public (Resources – GLOBAL MENTAL HEALTH PEER NETWORK (gmhpn.org)) on how to effectively engage with people with lived

experience and these guidelines should be looked at as opportunities for learning on how to proceed in transdisciplinary approaches in research. We all are still learning and there is great momentum with lived experience in research. I sincerely thank you for a great working relationship and hope to work with you soon again' said Claudia Sartor, Deputy Chief Executive Officer of an international lived experience organisation, the Global Mental Health Peer Network (GMHPN) and a lived experience expert and global mental health advocate fighting for the rights of persons with psychosocial difficulties.

Finally, the involvement of lived experience experts from Wellcome (Grace Gatera and Jamie Morgan) has also been instrumental in guiding us and ensuring that we have included PWLE aspects throughout the study and in the final report. Their expertise and perspective enriched our understanding and approach, reinforcing our commitment to inclusivity and relevance in mental health research.

6 Developers' decision-making processes

6.1 Overview

The R&D pathway for pharmaceuticals and medical devices is a complex, lengthy, and costly process involving multiple actors and stakeholders (see Section 4). For each intervention, developers must make decisions on whether (and how) to progress, refine or terminate development by balancing the risks and costs against the market opportunities and potential profits of the intervention. In this section, we review the key decisions that developers make in the context of the R&D ecosystem and as they navigate its different stages, namely discovery & pre-clinical, clinical, regulatory, and market launch.

The depiction and description of this is simplified to provide a broad overview and should not be interpreted as an exhaustive representation. Likewise, it is important to note that this process is not necessarily linear, and that the decisions made by developers are influenced by a multitude of external and internal factors, not all of which are included here. This is because the exact processes and decisions made concerning an intervention vary greatly and depend on the specific characteristics of the intervention and regulatory landscape in specific markets.

Lastly, it is worth noting that our interpretation and understanding of this progression is based on information gathered through desk research and anecdotal evidence collected through interviews with developers to formulate the case studies. Where relevant, we refer to concrete examples to contextualise the main processes and decisions, summarised and depicted in Figure 19. For the full case studies please see Appendix G to M.

6.2 Discovery & pre-clinical development

The decision to begin developing an intervention can be influenced by several reasons. Generally, it stems from an **exploratory investigation** where the goal is to identify an unmet need or problem, such as a lack of medication or medical device that could be used to prevent, diagnose, or treat a mental health disorder. Moreover, the motivation behind this investigation may itself be driven by personal reasons, as was partly the case for Inner Cosmos' development of the *Digital Pill* (Box 2), or by the commercial opportunities attached to the potential solution.

Box 2 Inner Cosmos Digital Pill

The Digital Pill is an implantable medical device for the treatment of depression, under development by the US startup company Inner Cosmos. It is based on the principle of an existing treatment method, Transcranial Magnetic Stimulation (TMS), which uses electromagnetic pulses on targeted areas of the brain. To resolve existing issues with patient access and adherence to treatment, Inner Cosmos is developing the Digital Pill to administer TMS via an implantable device rather than as a procedure at a health facility.

Inner Cosmos' co-founder and CEO Meron Gribetz was motivated by his own experience with pharmacological interventions to ADHD. Suffering from side effects because of the ADHD medication, Gribetz turned to think about mental health interventions which target only specific parts of the brain, leaving other parts unaffected. A neuroscientist by training with a background in technology startups (as founder and former CEO of a company developing augmented reality headsets), Gribetz decided to engage with clinical experts in laser neurosurgery (Dr Eric Leuthardt), neuropsychiatric BCI (Dr Darin Dougherty), and optogenetics (Dr Ed Boyden). Collectively, the team had extensive experience in entrepreneurship, in using a range of implantable medical devices for psychiatric conditions and in working with patients with treatment-resistant depression (i.e. patients who do not respond to pharmacological treatment).

The device is expected to benefit from building on an existing approach which has been approved for use and has been widely offered for the treatment of depression in the United States. The main concern for the developers is the sustainability of funding throughout the development pathway until commercialisation.

The exploratory investigation, commonly referred to as the 'ideation' or 'discovery' phase in the context of the innovation pipeline (Section 4.1 and Section 4.2), revolves around **identifying what the problem is and asking if it is epidemiologically and commercially worth solving**. The typical activities associated with this process involve devising a research plan or ideation strategy and deciding on set parameters to guide brainstorming sessions before narrowing down potential solutions and deciding to focus on those that *a priori* appear to be most viable and desirable. Table 19 below provides a summary of some of the unmet needs identified by each of the case studies and their proposed solutions/intervention.

Table 19 Case studies: unmet needs and potential solutions

Developer: Case study	Unmet need/Problem	Proposed solution/intervention
Boehringer Ingelheim (BI)	• Methods for diagnosing mental health conditions are inadequate	• Digital phenotyping for precision psychiatry and identification of novel biomarkers
GAIA: deprexis®	• Shortages of healthcare professionals following a significant increase in demand for mental health services as a result of the COVID-19 pandemic	• Web-based digital therapeutic platform providing psychological and psychotherapeutic therapies and exercises to assist patients in managing depression
Fisher Wallace Labs: OAK	• Alternative and more immersive, user-friendly treatment for depression	• Wearable neuromodulation device
gameChange	• Lack of treatment options for individuals suffering from psychosis and agoraphobia	• Immersive computer-generated simulations practised in a VR setting
Woebot Health	• Lack of treatment and care for adults living with mental health conditions	• AI-based conversational agent
Inner Cosmos: Digital Pill	• Individuals suffering from depression are unable to visit facilities where treatment is delivered	• Implantable medical devices for the treatment of depression based on Transcranial Magnetic Stimulation (TMS)
Psychedelics-based treatment for mental health conditions	• Lack of long-term effectiveness of current treatment options	• Psychedelics as an alternative treatment option for mental health conditions

Once the unmet need and potential solutions have been identified, the goal is then to formally **conceptualise the solution and determine its feasibility**. The developer would then need to decide on ways to carry out a market assessment to determine the commercial viability of the intervention, as well as a scientific assessment to determine its technical viability.

Specifically, the **market assessment**, on the one hand, involves an analysis

of the competitive landscape to identify any existing solutions or interventions to the problem identified, as well as any lessons learnt and monetary valuations of the existing treatment. Moreover, market assessments also involve creating potential customer profiles to identify who are the key beneficiaries of the potential solution and who would be the paying customers. Developers would then need to decide on ways to do this given available resources and budget constraints. Activities during this stage of the process typically require forms of fieldwork, such as consultations and surveys, and other forms of scoping analyses. At this stage, developers will also attempt to determine the scalability of the product and its potential return on investment (ROI). This is a key decision factor for continuing the development of an intervention. Overall, developers must be able to provide evidence that there is an existing market for the product (or a pre-agreed uptake from healthcare providers), that barriers to entry into the market are sufficiently low, and that the product can be profitable for the developer.

On the other hand, the **scientific assessment** typically involves creating a target product profile (TPP) for the potential intervention. The TPP will outline the desired characteristics and attributes of the potential new drug or medical product and the specific criteria that the product should meet to address the needs of patients, healthcare providers, and regulatory agencies. The more scientifically technical aspects of the TPP aim to provide preliminary indications on the usage (e.g. diagnosis, treatment, or prevention), dosage, route of administration, contraindications and adverse reactions based on similar products, and the optimal pharmacology of the medical product. Scientific assessments for pharmaceutical products will also consider whether the development of the drug is dependent on the existence of sufficient biomarkers and animal models. Given this information, developers would need to decide whether to continue building upon an existing intervention or developing a more innovative compound. This decision would often be influenced by developers' budget constraints and availability of resources to invest in R&D to identify new biomarkers and weighted against the estimated ROI of the potential intervention.

If the product is deemed commercially and scientifically viable, developers need to decide how to convert the idea into a more tangible concept. An **iterative process of prototyping and user testing** allows developers to determine whether the product is suitable and effective for its end users in a controlled environment. Having the funds to conduct smaller-scale pre-clinical testing of the product to account for critical failures is particularly important before moving to clinical testing for regulatory approval. The types of activities associated with prototyping and pre-clinical development can be in the form of bench studies, simulations, and *in vitro* and *in vivo* experiments that determine the pharmacology and toxicology of the medical product. Developers would also need to decide on **relevant**

stakeholders to consult throughout this process (e.g. PWLE, scientists, academics, manufacturers, regulatory authorities, etc.). A greater level of multidisciplinary co-production can have a positive impact on the potential of the intervention's success. To contextualise this, Box 3 summarises the discovery & pre-clinical processes (and by extension decisions) in the development of *gameChange.*

Box 3 gameChange

The gameChange development was led by a collaborative effort involving mental health professionals, academic researchers, virtual reality (VR) technology experts, and individuals with a first-hand experience of psychosis. The project was delivered by researchers at the University of Oxford and Oxford Health NHS Foundation Trust. Partners included Oxford VR, a University of Oxford spinout overseeing software development, the McPin Foundation, a UK charity which advocates for the involvement of people with lived experience (PWLE) in mental health research, the Royal College of Art, NIHR MindTech, and nine NHS Trusts across England.

The first step involved examining the prevalence rate and evaluating the extent to which people desired a change in the situation, as part of a comprehensive needs assessment. This included surveying 1,800 patients to identify the specific challenge of agoraphobic avoidance and determine its prevalence within the target demographic.

The design process was person-centred, incorporating the perspectives and needs of end users at every stage. The clinical psychology team in Oxford held overall responsibility for design decisions. The process included setting the initial design brief, conducting workshops, individual sessions, workflow production, scripting for the virtual therapist, prototyping scenarios for feedback, 3D modelling of environments, creating virtual characters, software implementation, extensive user testing, and quality assurance.

The next step involved developing a treatment brief which built on previous studies showing the efficacy of VR in treating anxiety in patients with psychosis. The treatment structure and delivery automation were influenced by prior VR interventions for fear of heights and persecutory delusions.

The input of users, particularly those with lived experience of psychosis, was central to design decisions. Over 500 hours of input were provided by 53 individuals. A Lived Experience Advisory Panel (LEAP) was established, consisting of ten individuals recruited from different centres participating in the clinical trial. They played a key role in defining the scenarios and providing ongoing feedback throughout design and development. Twelve design workshops were conducted in various locations together with McPin and the Royal College of Art, with participants providing input on scenarios, tasks, characters, and situational triggers. Individual user testing sessions and workshops with NHS staff further informed the development process.

In the subsequent script development of a virtual therapist, dialogues from both the virtual coach and other virtual characters were incorporated, as a vital component for automation. The psychology team identified and highlighted key fears and associated defence behaviours throughout the script, while role plays with and feedback from psychologists, developers, and PWLE were conducted and incorporated into the script. This process was repeated three times before the team reached the final script, which the LEAP reviewed and provided additional feedback on.

In the next step, the project team produced scenario workflows, where they mapped out user journeys. The LEAP team initially generated a list of situations relevant to patients, which included being on the street, using public transportation, and waiting in places like banks or doctor's offices, among others. Here, a key decision was to decide which scenarios and activities (people would undertake in those scenarios) to keep or exclude due to its feasibility to replicate in VR or relevance to anxious avoidance. This approach aimed to ensure that each trigger was integrated into one of the final scenarios. The final six gameChange scenarios that were selected were: travelling by bus, being on a street, visiting a café, going to a pub, waiting in a doctor's office, and shopping in a store.

The development process resulted in the creation of an automated delivery VR treatment. During this stage, there were several technical challenges such as maintaining a stable and high-quality virtual reality experience for users wearing headsets, addressing issues like drifting, which can cause discomfort or disorientation, and developing a procedure to decontaminate VR equipment during the COVID pandemic.

Throughout this stage, it is also common for developers to decide on the most adequate mechanism to safeguard the rights of the potential invention (i.e. the intellectual property, or IP). Some of the main forms of IP protection are patents, copyrights, trademarks, and trade secrets. Software-related inventions built on computing codes and algorithms may also opt for open-source protection. Similarly, at any stage of this phase of the process, developers will be faced with cost-related decisions that can ultimately determine whether to continue or terminate the innovation altogether. It is possible that a developer may have devised a novel solution to a problem affecting a large population, but it will not be able to continue if it does not have the funds to employ the labour and/or equipment that is needed to, for example, prototype the invention. If this is the case, developers could attempt to **raise the necessary funds** by seeking partnerships with private investors or investments from venture capitalists. For instance, in 2019 Fisher Wallace launched an equity crowdfunding campaign through the platform StartEngine to raise funds for *OAK* and has since raised more funds for its development through a seed investment firm (Box 4). Alternatively, developers may decide to apply for R&D funding made available through schemes and/or initiatives typically sponsored by public and other not-for-profit organisations. Interestingly, some of these initiatives are devised to incentivise or kick-start the very beginning of the process (i.e. the exploratory investigation).

Ultimately, the question that developers ask at the end of this stage is **whether the results from the initial tests are promising**. If they are, and developers can secure the necessary funds, the product can then be developed further and begin clinical development and testing.

Box 4 Fisher Wallace Labs OAK

Fisher Wallace Labs have been developing a wearable device for Cranial Electrotherapy Stimulation (CES) called Fisher Wallace Cranial Stimulator. It received FDA clearance in 1990 and achieved significant success by distributing 100,000 units, generating $40m in revenue between 2009 and 2023, with a pilot study in 2015 demonstrating rapid and significant decrease in depression symptoms for patients diagnosed with bipolar II depression.

However, as a result of the FDA's 2011 announcement, Fisher Wallace prepared to meet the new, more stringent, requirements by starting to develop a Version 2.0 wearable, called OAK. In 2019, Fisher Wallace launched its first equity crowdfunding campaign through the platform StartEngine to raise funds for OAK. Approximately 4,500 individuals have invested via the platform, including thousands of current users of the Fisher Wallace Stimulator, who collectively now own approximately 15% of the company. Since 2019, the company has raised over $9m through equity crowdfunding, signalling high customer interest for OAK. In addition, the company received approximately $3m in investment from SHUFL Capital, a UK-based seed investment firm focused on businesses in the areas of sleep, health, fitness and leisure.

Kelly Roman, CEO of Fisher Wallace, worked with designers from Microsoft and Beats Headphones for two years to develop a wearable with perfected stimulation and form factor (e.g. shape and configuration). The patent-pending technology was designed to be as affordable, attractive and user-friendly as possible and is now a completely head-worn wearable with integrated electrodes. Available in multiple colours, OAK will allow patients to choose the colour of their depression treatment. OAK will also be Bluetooth enabled, with a speaker for voice assistance during use. In addition to the design changes, the newer version has a fixed output, set at the optimal amount of electricity for effectiveness, safety and comfort, compared to the first version that allowed patients and providers to vary the output themselves, within a range of 0-4 mA. Fisher Wallace is also developing a companion app that will be able to track symptoms, as well as cognitive performance. The developers are looking at integrating talk therapy and curate other digital health services through this app, for customers who would benefit from an additional intervention at an affordable price.

6.3 Clinical development

The type of clinical development and testing that is required for the intervention is dependent on the specific characteristics of the product and on the types of regulatory approval that it requires before receiving marketing authorisation. This will vary in accordance with the regulations imposed by the relevant regulatory authorities in the country where the developer hopes to commercialise the product. Generally, pharmaceuticals will require more rigorous **testing via clinical trials** while medical devices are first subject to a **risk-based assessment** to determine how it will progress through the clinical stage of the R&D ecosystem.

The risk-based assessment for medical devices (both digital and non-digital) considers the potential risks to patients from using the device and can be broadly categorised into three classes: low, moderate, and high. The amount of oversight from the regulatory authority will be greater as the risk to the patient increases. At this stage, guided by regulatory requirements and budgetary constraints, developers must decide on appropriate methods to gather data on the usability and

potential risks of the device, as well as its functionality and biocompatibility. This can be done in a clinical trial setting, though not necessarily fall into a defined clinical trial Phase. For instance, in testing the efficacy of *Woebot*, developers showed through an RCT with 70 participants that young adults reported a greater reduction in depressive symptoms when they used the product, while those in the control group did not (Box 5).

Box 5 Woebot

Woebot is an automated conversational agent (chatbot) delivered to patients on a smartphone. It is designed to provide support and resources for individuals dealing with a range of mental health challenges, such as stress, anxiety, and depression. It uses principles from cognitive behavioural therapy (CBT), interpersonal psychotherapy (IPT) and dialectic behavioural therapy (DBT) to deliver therapeutic interventions. In various studies, Woebot has demonstrated to be a feasible and engaging relational agent to improve users' mental health conditions. There are currently three distinct solutions on the market: Woebot for Adults, Woebot for Adolescents, and Woebot for Maternal Health. The latter is the first digital therapeutics designed to reduce the burden of postpartum depression and it has been granted a Breakthrough Device Designation by the US FDA. Woebot solutions have however not been evaluated, cleared or approved by the US FDA.

Key success factors for developing Woebot include the engagement of a diverse group of experts, such as clinical psychologists, conversational writers and software developers, and people with lived experience. Woebot Health has secured capital from multiple investors, amounting to a total investment of $123.5m to date.

Woebot Health has been conducting several clinical trials for their interventions, both non-randomised open label studies and double-blind, randomised control trials (RCT). Woebot Health noted that generation of evidence on effectiveness under traditional RCT conditions is challenging as these do not align well with real-world scenarios. Another challenge is to reach patients in the heterogeneous landscape of healthcare providers and associated health systems in the USA, impeding smooth market entry for the developer. However, due to their partnerships with PayrollPlans and with Virtua Health, the company has now access to millions of potential users.

Woebot interventions are currently offered to patients through a non-prescription access pathway. Woebot Health distribute their products to patients in the USA via partner organisations, such as virtual primary care companies, payers and integrated delivery networks. As of September 2023, nearly 1.5 million people have downloaded Woebot.

As next steps, the company is exploring two routes to expand access to patients: (i) tackling new conditions such as individuals struggling with substance use; and (ii) focusing on a fast-growing non-prescription pathway while being open towards a prescription pathway in the future.

For devices considered to be of high risk that require clinical trials to demonstrate their efficacy and safety, the decisions made by developers of medical devices would be similar to those made by drug developers. The processes and decisions developers are faced with when conducting clinical trials can be significantly more burdensome and lengthier. Firstly, clinical trials need to be thoroughly designed. Developers must decide on the approach to the clinical trial, including whether it is feasible to conduct an RCT or single-arm trial, blind testing, and the availability of a

placebo for a control group, among other considerations. For instance, placebos can prove challenging with respect to psychedelics as a potential treatment for a mental health condition as participants can quickly identify if they are in the treatment or control group and may thus opt out from the trial altogether.

The clinical trial design process also requires developers to define the selection criteria for trial participants such that it is as representative as possible, length of study, and method of analyses. In particular, the challenges associated with recruitment to trials may prove critical in deciding whether the developer goes through with the innovation. For example, in the case of Boehringer Ingelheim, the transdiagnostic approach used to identify potential interventions, created difficulties in the trial recruitment as there was no way to select participants who had the specific biological difference being investigated. Depending on the severity of the challenges and barriers faced throughout the clinical trials (e.g. low retention rates, delays, etc.), the developer may reconsider its trial design or decide to forgo the intervention entirely.

All in all, many of the decisions that medical developers make at this stage are predominantly imposed by external factors (i.e. the regulatory conditions), which in principle would have been anticipated during a feasibility study. That being said, developers may not proceed with clinical development if the administrative and testing requirements for the medical device become too burdensome and more costly than originally anticipated.

In the end, the reason for clinical testing is to determine **whether the product is effective and safe** as these are determining factors for any type of intervention. Developers will be forced to rethink the intervention entirely if it is found to be inefficient and/or unsafe in clinical trials, while a lower efficacy would pose a higher risk to the product being granted the necessary regulatory approvals and generating the expected ROI.

6.4 Regulation

Once testing has generated enough evidence to show that the product is safe and effective, developers must prepare the necessary **regulatory applications** to health authorities. This may involve consultations and other pre-submission meetings with regulatory bodies to ensure and confirm the types of necessary documentation for developers to decide on the most appropriate regulatory pathway. Note that consultations of this type are likely to take place prior to beginning the clinical phase. In some cases, there may be existing guidance to aid this process, which may be of particular help for first-time applicants and SMEs, or where the regulatory pathway is somewhat vague as is the case with some forms of digital health technologies such as well-being apps.

As explained previously, regulatory approval can pose a significant barrier or be a delaying factor in the development pipeline for medical devices, but the process can be expedited if there is precedent for a

similar intervention receiving regulatory approval. A caveat of this, however, is that the more innovative interventions are impacted the most at this point. For pharmaceuticals, as explained previously, safety is a key influencing factor at the time of regulation. Alternatively, in the case of Boehringer Ingelheim, promising results showed in Phase II of the trials meant that one of the products in its pipeline (*iclepertin*) was granted Breakthrough Therapy Designation by the FDA to help expediate its development and regulatory review.

Part of regulatory approvals may also involve establishing manufacturing process and quality assurance systems. It is important for developers to consider that not all technologies developed in academic settings and tested in controlled environments can be made easily using mass manufacturing techniques. Developers need to devise and make decisions on the materials and production processes that can ensure safe handling and comply with environmental regulations, among other considerations, to be approved by the relevant legislative authorities. In the case of digital health technologies and software development, developers must also be able to demonstrate that the innovation has the appropriate safety and privacy features to protect patient health and other personal information. This was the case in the regulatory approval of deprexis® in Germany where all data processing in connection with the use of the product must remain in Germany (Box 6).

Lastly, a Health Technology Assessment (HTA) may be carried out to assess the suitability and cost effectiveness of the intervention to guide the pricing and reimbursement negotiations prior to market launch.

Box 6 deprexis®

deprexis® is a web-based digital therapeutic platform developed by GAIA, offering evidence-based self-help programmes for managing unipolar depression or depressive disorders. It includes ten modules with various resources, such as worksheets and exercises, adapting its approach to user preferences. Available in multiple markets, including the UK, the US and Germany, deprexis® can be accessed through subscription or prescribed by healthcare professionals as part of depression treatment. The platform was tested in several randomised clinical controlled trials (RCTs), which showed that it was effective in treating symptoms ranging from mild to severe. deprexis® has been approved in the UK (partially), the US and Germany.

The three main markets for deprexis® are Germany, the US, and the UK. Therefore, deprexis® is required to obtain marketing authorisation in these three countries. The regulatory approval process for digital therapeutics is relatively new, and in some countries, the requirements and classifications are still unclear, which can be challenging for developers to navigate.

In Germany, it navigated the Digital Health Care Act (DVG) and secured a spot in the DiGA directory, leveraging a Fast-Track Process overseen by the Federal Institute for Drugs and Medical Devices. This facilitated its approval as a browser-based web application, with all data processing mandated to remain within Germany.

In the US, the FDA's Digital Health Center of Excellence and an Enforcement Policy for digital health devices, prompted by the COVID-19 pandemic, provided a pathway for temporary approval via the Emergency Use Authorisation. Although this authorisation was temporary, guidance was issued for transitioning to normal operations post-pandemic.

In the UK, the Early Valuation Assessment (EVA) programme, introduced to expedite the assessment of digital technologies, became pivotal. Identified as a priority area, mental health technologies like deprexis® underwent evaluation. Following positive outcomes, the next phase involves collecting real-world evidence in collaboration with NHS providers, such as The Grange Medical Centre, to support a full NICE assessment. This collaborative effort aims to bridge evidence gaps and ensure the integration of deprexis® into routine clinical practice, with ongoing pilot programmes in regions like Warwickshire, Leicester, and Liverpool.

6.5 Market launch

Having achieved marketing authorisations, the developer's decisions prior to the full market launch would be around pricing and reimbursement. As explained previously, the results from an HTA may help to guide these negotiations. Before the full market launch, developers, public authorities, and healthcare providers would also discuss arrangements to establish distribution channels. This includes, for instance, whether the uptake of the drug or medical devices will be distributed by private or public healthcare providers and how customers can access the intervention (e.g. over-the-counter vs. prescription) and whether insurance providers will cover the costs of the intervention. In the case of *Woebot*, the service is available as a non-prescription device in order to reach as many users as possible, which offered relatively rapid market entry and reduced regulatory burden, but it also limits market credibility and reimbursement opportunities (Box 5).

In the case of deprexis®, the product can be prescribed by doctors or

psychotherapists in Germany and costs covered by patients' health insurance, while in the US a prescription is not necessary for patients to access deprexis®.

At this stage, the developer would also need to decide and deploy a marketing strategy to promote its product or service. Part of the developers' promotion strategies may require educating healthcare professionals and patients on how to administer and use the drug or medical device. This can be done, for example, by preparing toolkits, online guidance, hospital visits from pharmaceutical sales representatives, at medical conferences, and so on. For instance, Boehringer Ingelheim has reportedly developed an immersive pop-up campaign to demonstrate the impact that cognitive difficulties can have on an individual's daily life and raise awareness and understanding of the whole spectrum of schizophrenia symptoms (Box 7).

Provided that there is enough consumer demand, it is fundamental that developers have the capacity to engage in post-market monitoring activities to continue ensuring the safety and efficacy of the drug or medical device. Where possible, developers may be able to introduce upgrades to enhance the usability of medical devices based on customer feedback. Moreover, there may be additional side effects that were not captured during clinical trials. Depending on their severity, developers may be forced to withdraw the product from the market altogether.

If the innovation has **proven to be effective and profitable**, developers would then be in a position to decide whether **scale up production** and, if desired, attempt to **commercialise the product in new markets**. In the case of the latter, this would entail going through the regulatory processes and safeguards in the target market, or even through clinical testing if the safety and efficacy evidence is not deemed to be sufficiently convincing.

Box 7 Boehringer Ingelheim

Boehringer Ingelheim (BI) is a German pharmaceutical company that has a steadily growing pipeline of drug interventions in their pipeline. BI are currently combining 'precision psychiatry' and a transdiagnostic approach in order to develop effective pharmaceuticals by focusing on the individual variability of mental health conditions rather than being restricted by the traditional single-diagnosis approach.

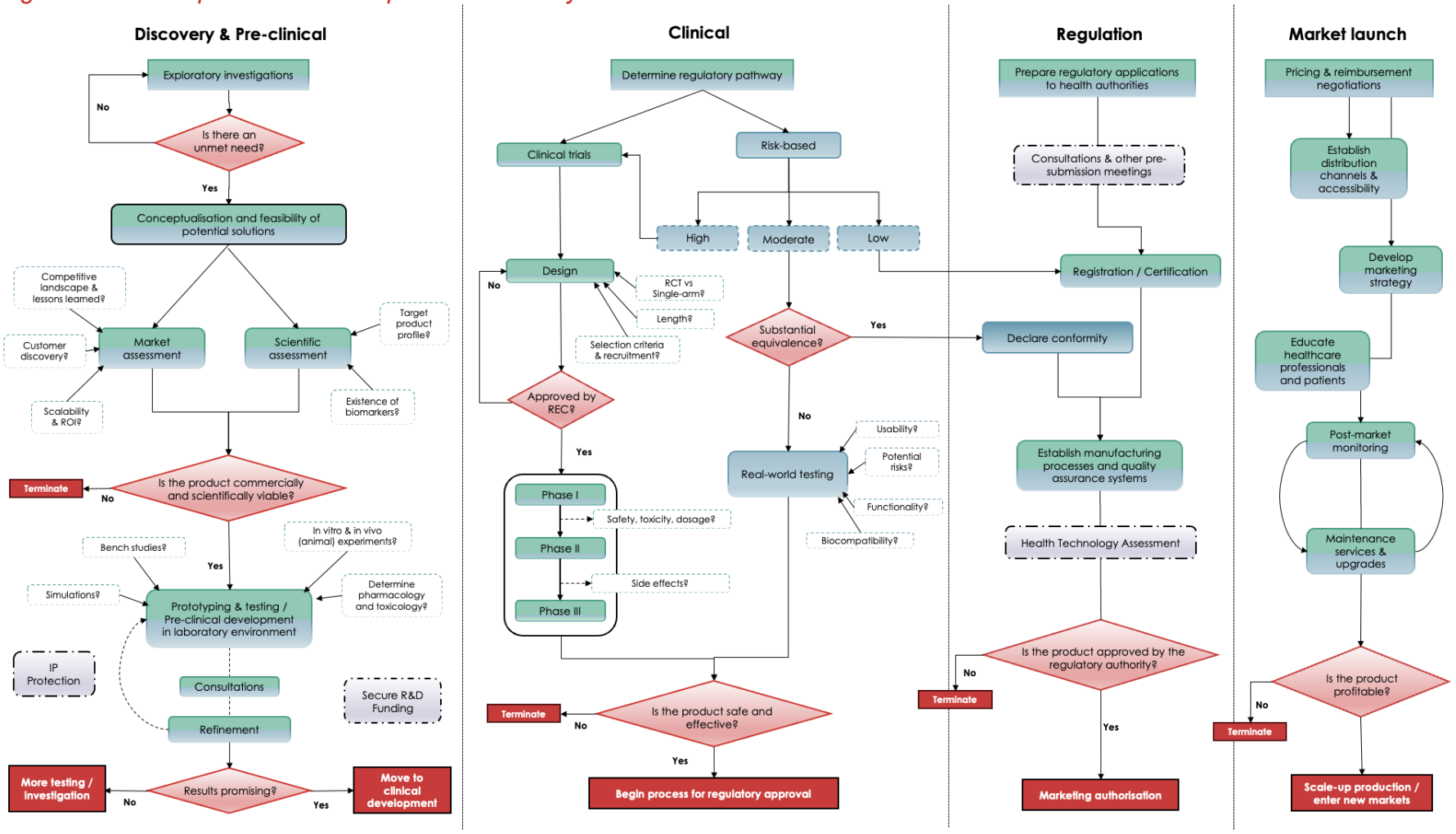
BI currently have pharmaceutical interventions in their pipeline for the treatment of symptoms relating to Major Depressive Disorder (MDD), PTSD, schizophrenia, and Borderline Personality Disorder (BoPD), as well as complementary digital therapeutics.

Patients with Major Depressive Disorder (MDD), schizophrenia, and Borderline Personality Disorder (BOPD), were found to all share a common abnormality in the amygdala and BI are therefore developing a TRPC4/5 inhibitor to reduce the associated emotional symptoms in all three conditions. If successful, this drug would therefore be able to improve the symptoms of a larger population. However, there have been difficulties in recruitment for clinical trials as the developers ideally only want to include patients with the specific biological abnormality.

BI have also consulted PWLE to determine the mental health symptoms with the most significant day-to-day burden. The majority of people with schizophrenia experience cognitive difficulties, but due to the stigma around the disease, interventions relating to psychosis are prioritised over treatments for other symptoms. BI are therefore developing what would be the first pharmaceutical that reduces these cognitive symptoms in schizophrenia, and would have a significant impact on the quality of life for these individuals. To provide more holistic treatment, BI have partnered with Click Therapeutics to also develop a digital intervention that supports patients in reducing the negative symptoms of schizophrenia.

While the pharmaceutical intervention that BI is developing would meet a clear unmet need, there are also challenges that come with this. Schizophrenia is a condition with high levels of stigma associated with it compared to depression and anxiety, and BI have experienced difficulties in recruitment for clinical trials due to this. They are also concerned about uptake by clinicians in the future, as reducing cognitive difficulties is not seen as a priority. BI developed an immersive pop-up campaign to demonstrate the impact that cognitive symptoms can have on an individual's daily life, in order to improve education and awareness.

Figure 19 Developer Decision Map: R&D Pathway



Source: Technopolis

7 Barriers in the mental health R&D ecosystem

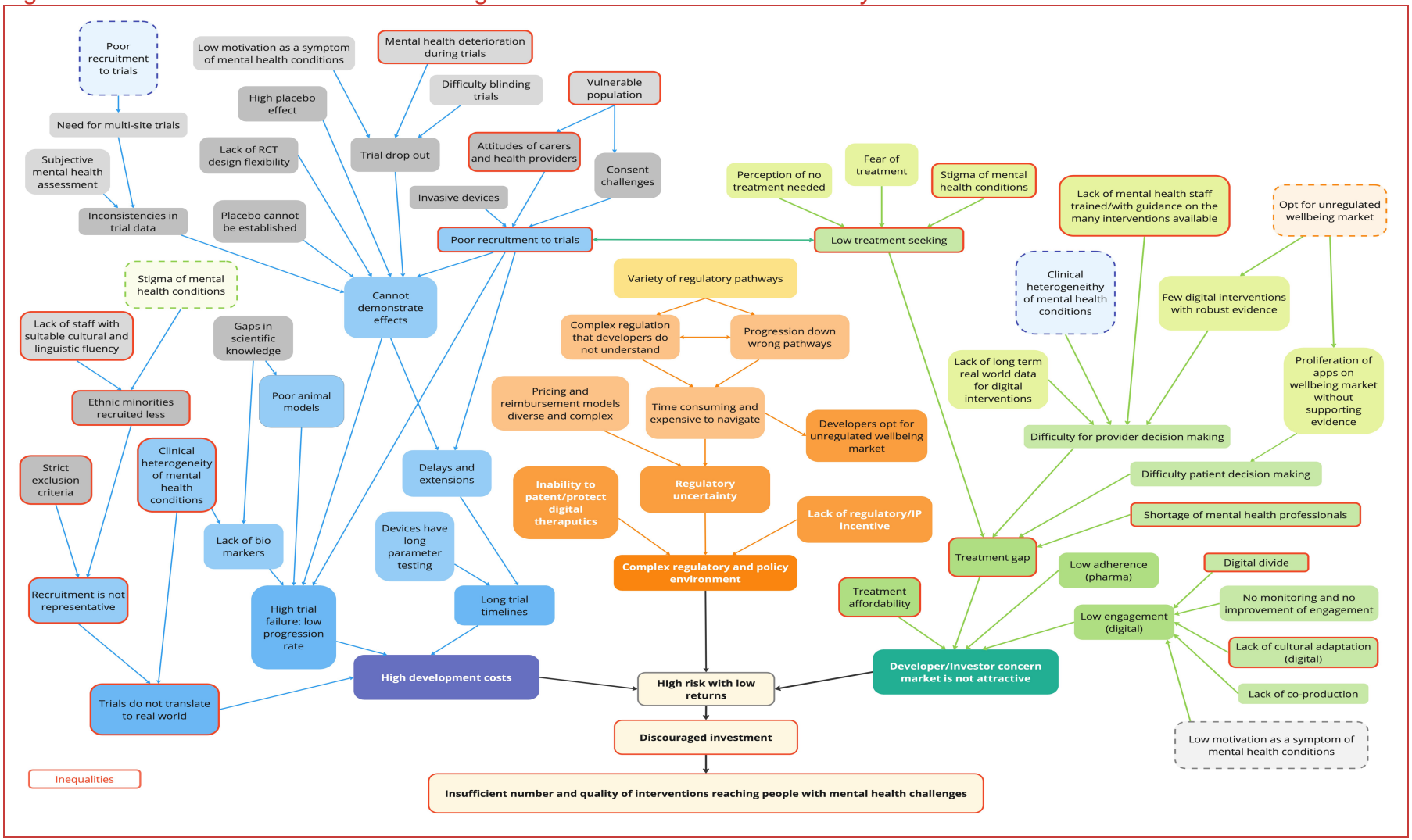
The progress of interventions (e.g. pharmaceuticals, behavioural therapies, medical devices and digital therapeutics) along the pathway from bench to patient use may encounter challenges at various steps. While the scientific challenges are relatively well documented (see Appendix B), there is much less shared understanding among the mental health community on the non-scientific challenges that are acting on the ecosystem (see Appendix D).

The triangulation of the evidence gathered via the literature reviews, interviews, and quantification exercises has highlighted a range of scientific and non-scientific challenges in the mental health R&D ecosystem, with a focus on the subset of challenges that are blocking progress (barriers). We have assigned each barrier into three overarching categories that are related to development costs, the regulatory and policy environment, and the mental health treatment market.

These barriers may directly impact on R&D outcomes in the mental health R&D ecosystem, influencing the overall level of return. The (partly perceived) high risk discourages investment, resulting in an inadequate number and quality of interventions reaching people with mental health challenges.

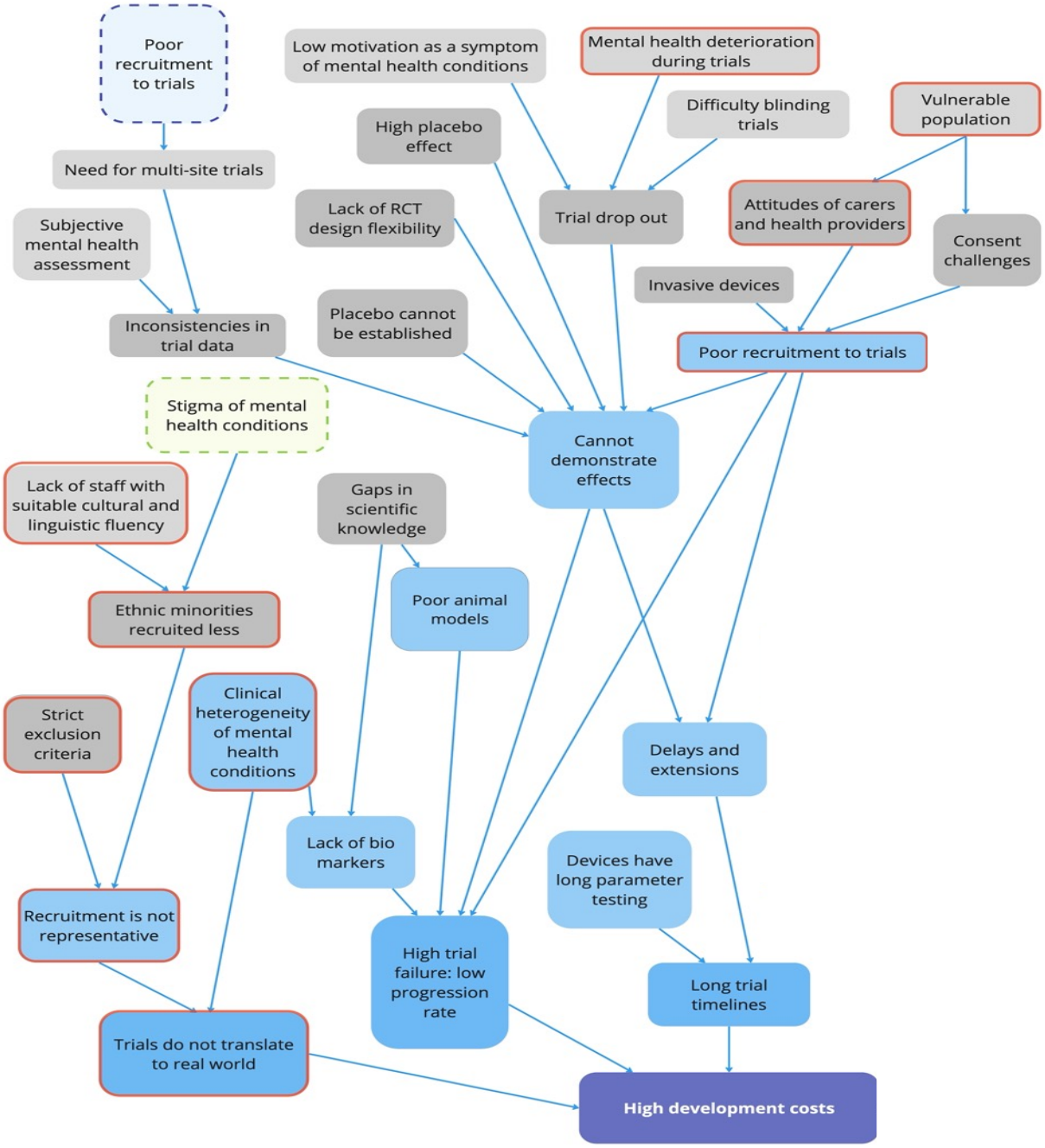
Figure 20 presents an overview of the barriers in the mental health R&D ecosystem identified in this study, illustrating their interlinked nature.

Figure 20 Overview of barriers and challenges in the mental health R&D ecosystem



Source: Technopolis. Key: blue and grey are related to high development costs, orange is related to regulations, and green is related to unattractive market.

7.1 High development cost



The literature review and stakeholder interviews in this study highlighted that clinical trials for mental health interventions encounter a set of specific challenges increasing the risk of delays, heightened costs and trial failures or terminations. Key challenges identified contributing to high failure rates of mental health clinical trials prior to completion include:

- **Lack of biomarkers and animal models to robustly measure the effects of mental health**

interventions. Despite advances in the field of basic neuroscience, much remains to be understood to establish the links between molecular and cellular mechanisms and mental health symptoms. The limited knowledge of underlying disease mechanisms of mental health conditions has made it difficult to identify biomarkers to objectively measure the biological effects of mental health interventions.[76–87] Furthermore, modelling complex mental health conditions in animals is extremely difficult due to differences in brain anatomy, neurological pathways and behavioural capabilities between animal models and humans. The lack of robust and standardised set of biomarkers and animal models pose key challenges for the development of mental health interventions, as their effects cannot be measured robustly, which can lead to clinical trial failures.

- **Clinical heterogeneity of mental health conditions.** Contrary to other health conditions that are classified by common molecular mechanisms of action, mental health conditions are classified by diagnostic categories (e.g. International Classification of Diseases [ICD] or Diagnostic and Statistical Manual of Mental Disorders [DSM]) with a broad variety of clinical symptoms, comorbidity and underlying mechanisms. Consequently, subgroups of patients within a mental health condition may respond differently to the same mental health intervention, which can lead to inconsistent results and clinical trial failures.[88]
- **Clinical trial recruitment and retention challenges**. Developers of mental health interventions highlighted poor recruitment and patient retention is a key reason for mental health clinical trials delays or terminations. Recruiting patients with severe mental health conditions can be particularly challenging due to stringent eligibility criteria.[89,90] Retention of trial participants in mental health is generally more challenging than in other fields, and the drop-out rate tends to be high. Decreased motivation is a core feature of many mental health conditions, which can make it challenging for participants to consistently engage in mental health clinical trials.[91] Furthermore, mental health patients with significant functional or cognitive impairments may find it difficult to regularly engage in clinical trial activities. Some patients may experience side effects or perceive a deterioration in their mental health and decide to drop-out of clinical trials.
- **Challenges designing appropriate placebo:** Designing a placebo can be problematic for clinical trials of mental health digital and non-digital devices as it is often not feasible or possible to design an adequate placebo as they are complex in their design.[92–95] Digital therapeutics can integrate many features such as symptom tracking, goal setting, community support, and psychoeducation content.

Therefore, it is challenging to construct a plausible placebo by excluding or altering the main features. Designing a placebo for mental health devices can also be challenging. Typically, a 'sham' placebo control is designed which is an ineffective device designed to mimic active device stimulation. However, sham stimulation is found to be not entirely equivalent to non-treatment condition. Failure to design an appropriate placebo can compromise the validity and reliability of the clinical trial results, potentially leading to trial failure.

- **High placebo effects**, i.e. the improvement of symptoms in response to a placebo, can reduce the observed treatment effect, which can make it challenging or impossible to detect significant differences between the active treatment and placebo, leading to clinical trial failures. Clinical trials of mental health pharmaceuticals have been associated with high placebo effect. A study in 2022 showed that the placebo effect could be as large as 70-90% in mood disorders and 50-60% for schizophrenia.[23] Factors associated with larger placebo effects include 'expectation bias' of participants who have positive expectations that the treatment received may be beneficial.[96–98]

We conducted a quantitative exploration of Trialtrove data to investigate reasons for failures of pharmaceutical trials for mental health conditions. It revealed approximately 13% of the 2,976 clinical trials for pharmaceutical products targeting anxiety, depression and/or psychosis terminated before completion (375 trials), with 267 trials providing reasons for their termination. Notably, 96 trials (36%) included in the analysis reported more than one reason for termination, highlighting the complexity and interconnected nature of challenges faced in advancing mental health research. The reasons for termination exhibit similar distribution across the three mental health conditions, showing no disproportionate impact of any one specific reason on a particular type of condition (Table 20).

Around a third of all terminated trials with information on the reasons for termination reported instances of trials being planned but never initiated (89 out of 267 trials). Clinical trials are included in this group if they are initiated but have not had any development reported in two years or more. Of these trials, only two have provided further details on the reasons behind the termination, citing that the trials were not initiated due to negative results in similar trials or pandemic-related challenges impacting clinical trial sites and/or potential participants.

Furthermore, around 22% of terminated trials for mental health conditions (58 trials) stated that the reason for termination is due to a business decision, including the need to reprioritise the developer's R&D strategy.

Around 16% of terminated studies (44 trials) pointed to **poor enrolment of patients** as the reason for termination, failing to reach the statistical power necessary to detect any treatment effects.

According to our analysis of Trialtrove data, slightly less than half of all Phase I clinical trials for mental health conditions met their patient enrolment target, compared to only around a quarter of Phase II and Phase III trials.

Table 20 Reasons for termination of pharmaceutical trials, 2013-2023

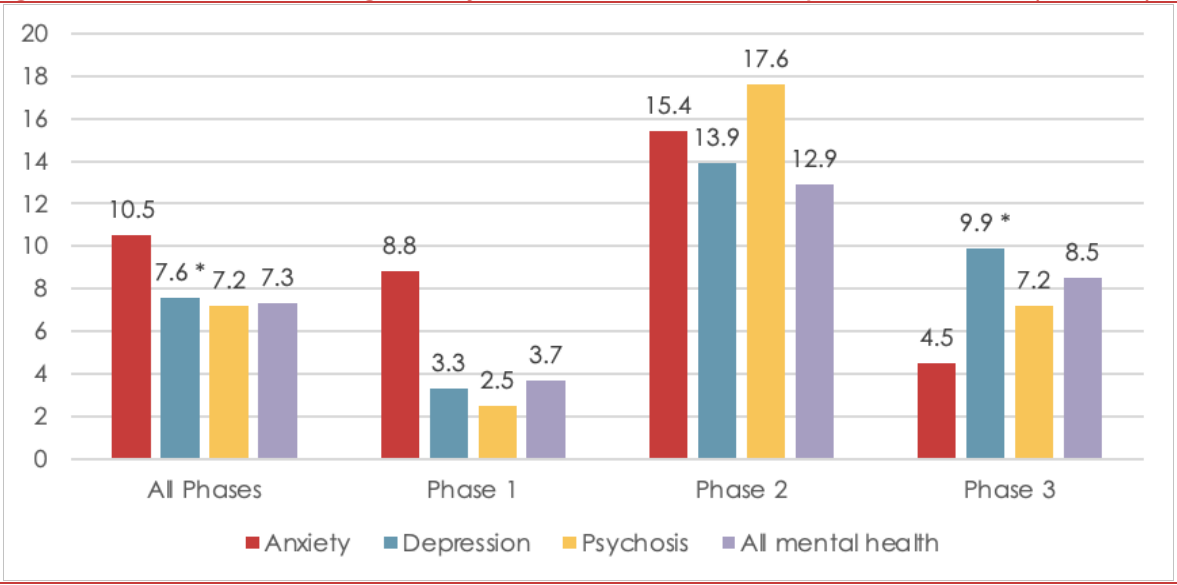
	Anxiety	**Depression**	**Psychosis**	**All mental health**
Number of trials	627	1,501	1,221	2,976
Number of terminated trials	90	182	144	375
Number of terminated trials with reported reason for termination	61	131	98	267
Planned but never initiated	39%	31%	32%	33%
Business decision	16%	24%	21%	22%
Poor enrolment	13%	18%	16%	16%
Lack of funding	8%	11%	7%	9%
Lack of efficacy	8%	2%	3%	4%
Safety/adverse effects	2%	4%	3%	3%
Other	54%	82%	81%	75%

Source: Trialtrove. *Note: One clinical trial can record multiple reasons. The sample excludes terminated clinical trials without information on the reason for termination.*

We used information on the enrolment shortfall and enrolment duration per patient to estimate the number of additional months that would be needed to meet the enrolment target. This can be interpreted as a proxy for the average delay of completed clinical trials due to poor enrolment.

Figure 21 shows how this delay varies across the different phases and conditions. Across all phases, the average delay in clinical trials was 10.5 months for anxiety disorders, 7.6 months for depression and 7.2 months for psychosis.

Figure 21 Estimated average delay of clinical trials due to poor enrolment (months)



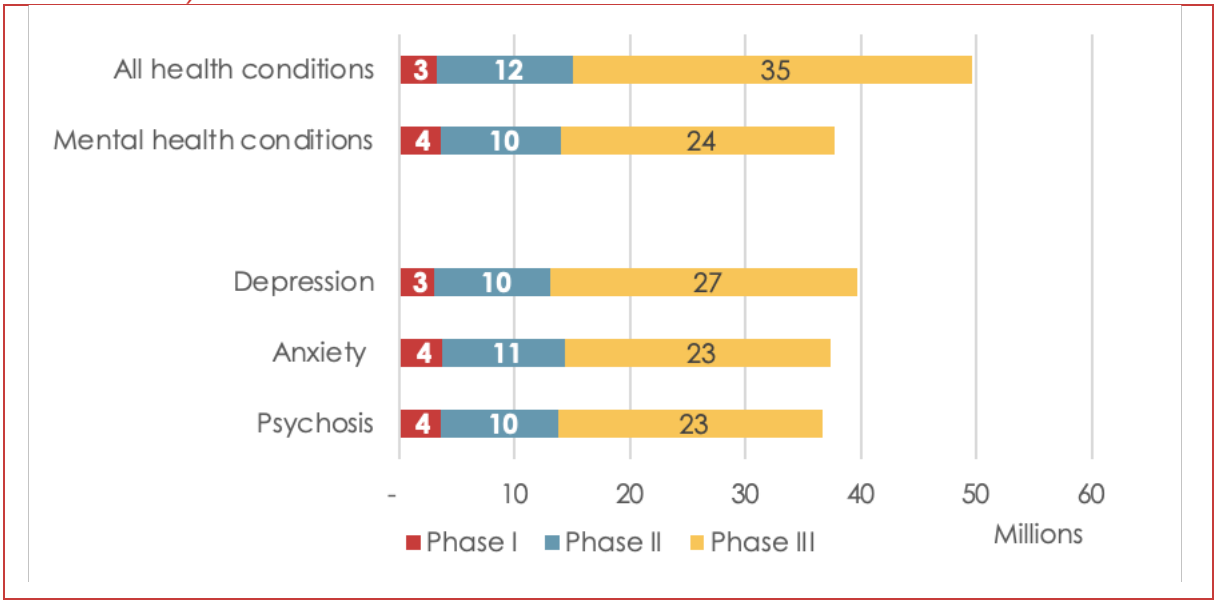
Source: Trialtrove; *Note: the average delay of clinical trials due to poor enrolment is calculated as the product of the enrolment shortfall (i.e. actual enrolment minus target) and the enrolment duration per patient (i.e. enrolment duration in months divided by the number of patients enrolled). Calculations are authors' own. Note: *The estimates exclude three large outliers of clinical trials that set out ambitious enrolment goals (>1,000 patients per trial) and subsequently failed to achieve a substantial portion of their intended target. When these outliers are included in the analysis, the average delay is 115 months for Phase 3 depression trials and 26.3 months across all depression trials.*

Additionally, we conducted a quantitative exploration of Trialtrove data to gain insight on the average clinical trial costs per phase for mental health conditions compared to other health conditions. Data for the average cost of medical devices clinical trials was not available for this study and, as such, our analysis explores the average costs of pharmaceutical clinical trials only. The analysis reveals a pattern across different phases of development, with an expected escalation in costs as drugs progress in their development journey. Phase I trials, which involve initial safety assessments and relatively small sample sizes of patients, incur an average cost of $3.6m across nine different mental health condition (n=1,066), compared to an average of $3.3m for all health indications (n=29,460). As trials advance to Phase II, where preliminary efficacy is assessed in larger patient cohorts, the average cost of mental health clinical trials can rise to $10.4m (n=449), compared to $11.8m on average across all health conditions (n=27,151). The most substantial increase is observed in Phase III, where comprehensive efficacy data is collected from an even larger sample of patients, potentially reaching an average cost of $23.7m on average across nine mental health conditions

(n=268), compared to $34.5m across all health conditions (n=12,270).

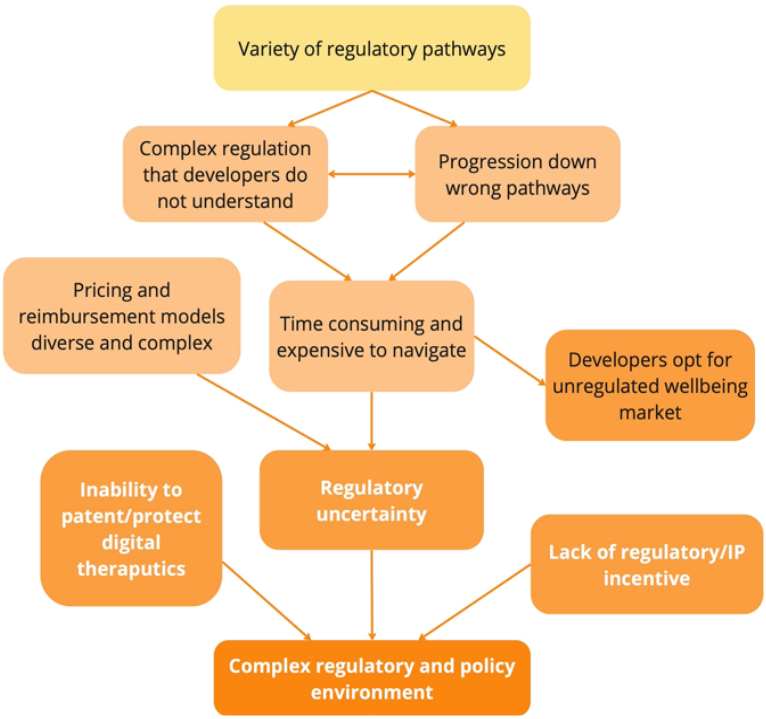
While mental health clinical trial costs are not higher than other health conditions, this high cost in the absolute is part of the overall R&D expenditure for developing a mental health solution and need to be considered relative to expected returns. Large pharmaceutical companies could be able to afford these clinical trial costs, but smaller innovative companies would struggle. Therefore the 'high development cost' should be considered as 'unaffordable' for some developers.

Figure 22 Average clinical trial costs ($ million), per phase and indication (2018–2023)



Source: Citeline estimates using Trialtrove data and published research. *Note: Trial phase specific costs were taken from Sertkaya et al. (2016),* [4] *and back calculated to provide a per patient cost for all three phases. The per patient costs were then multiplied by trial recruitment data from Trialtrove to provide trial specific costings for each relevant indication. Per trial and per site costs provided in Sertkaya et al. (2016) were added accordingly without adjustment or back calculation*

7.2 Complex regulatory and policy environment



Developers, funders and investors highlighted that uncertainty around the level of regulatory evidence requirements for mental health interventions can be a barrier to their development and adoption. Other barriers included a lack of standardised ways to collect real-world evidence on the effectiveness of mental health digital therapeutics to build the evidence to support their adoption in healthcare systems.

The regulatory process for digital therapeutics, is perceived as extremely complex by developers. Consequently, many **developers opt to focus on the well-being market rather than navigating the complex regulatory landscape**. This trend has led to a surge in well-being apps claiming to enhance various aspects of mental health. This proliferation, however, raises concerns within the field, especially when compared to evidence-based digital therapeutics designed to address specific mental health conditions. A systematic review of over 1,000 publicly available well-being apps revealed that only 2% have peer-reviewed research evidence supporting their efficacy.[99]

Developers of devices described **navigating evolving medical device regulatory evidence requirements in different countries as a key barrier**, leading to delays in achieving widespread approval. [100–102]

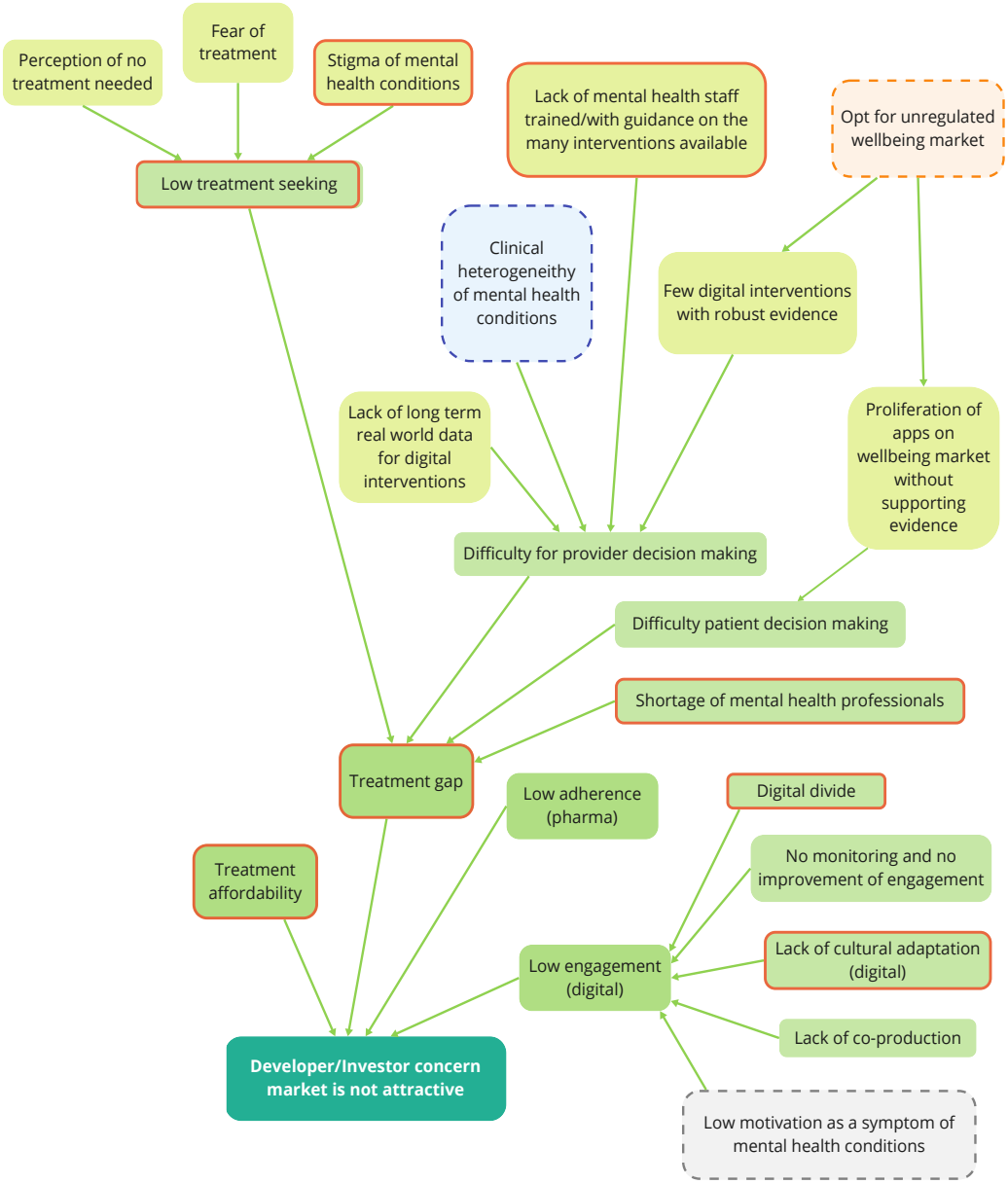
In the mental health field, combination products, incorporating elements from various therapeutic types, are becoming more prevalent.[103] These could involve a blend of pharmaceuticals, devices, or digital therapeutics. The regulatory uncertainty surrounding combination

products poses challenges, as different systems may allocate them to various or multiple pathways, often handled on a case-by-case basis.

Moreover, developers highlighted that the **lack of flexibility** in current UK regulations is impeding the development and advancement of psychedelic-based treatments for mental health conditions. The primary issue stems from the regulatory classification of these drugs, with psilocybin and psilocin falling under the Misuse of Drugs Act 1971[104] as Class A drugs and categorised as Schedule 1 controlled drugs following the 2005 regulation amendment.[105] This classification renders them illegal and deems them to lack medical value. Groups seeking to conduct research on the therapeutic potential of psychedelics must acquire a Home Office licence and coordinate extensive security arrangements (see the psychedelic case study Appendix M).[106]

The literature review and interviews with stakeholders did not indicate any specific regulatory challenges regarding the development of mental health pharmaceuticals.

7.3 Unattractive mental health treatment market



Developers and investors do not perceive the mental health market as attractive because there is uncertainty about the return on investment (ROI) for mental health interventions. There is a treatment gap in the area of mental health – a low number of people are receiving treatment compared to the number of cases. Many people with mental health conditions do not seek treatment or are not able to access it due to a shortage of mental health professionals. For those accessing interventions, mental health pharmaceuticals can have poor adherence rates and there can be low engagement levels with digital tools. Key challenges identified contributing to low ROI for mental health interventions include:

- **Limited market size for mental health interventions**. Despite the high prevalence of mental health conditions, only a relatively low proportion of people seek treatment. This limits the potential market size and ROI of mental health interventions. It is estimated that 40% of patients living with schizophrenia, 50% of patients living with bipolar disorder, and 35% of patients living with major depression do not seek treatment.[2] The World Mental Health Surveys, conducted in 24 countries with over 6000 responses, found that lack of perceived need for treatment was by far the most frequently reported reason given for not seeking treatment for mental health conditions.[63] A recent publication reported a key reason why people fail to seek mental health treatment is because they 'interpret their psychological and emotional states as reactions to social and economic problems, not as health conditions' that can be addressed by mental health interventions.[64]
- **Stigma** associated with mental health conditions is a major factor contributing to the low proportion of patients seeking treatment for mental health conditions. Stigma appears to be a stronger barrier to mental health treatment access within low-resource areas and among vulnerable members of the population including poor and ethnic minorities. [107–111] A systematic review of barriers to the recruitment of ethnic minority participants into mental health clinical trials reported stigma related to being 'labelled mentally ill' may be a comparative greater deterrent in ethnic minorities compared to the general population.[112] Healthcare professionals in both high-income countries and LMICs can have stigmatising beliefs, attitudes and discriminatory behaviours towards people with mental health conditions. Such stigmatising attitudes undermine access to treatment for people with mental health conditions. Additionally, it contributes to the **reluctance of people to seek help** for mental illness.
- **Poor adherence to mental health interventions** is recognised as a common problem that limits the potential market size and ROI. A multitude of factors can influence adherence to mental health pharmaceuticals such as patients' social and demographic

characteristics, education level, cultural context, negative attitudes toward medication, treatment side effects, lack of medication routines, fear of addiction, poor patient and clinician interaction, and unsupportive social networks.[113,114] Digital mental health interventions can have low adherence and engagement rates. The lack of co-production between the developers, end users, researchers and clinicians to develop digital therapeutics that are tailored to the needs of people with mental health conditions is a reason for low engagement. [68–72] Furthermore, the 'digital divide' is amplifying inequalities for people with mental health conditions who have limited ability to engage with mental health digital therapeutics either because they do not have access to the internet or the skills to engage with digital content.[115,116]

- **Shortage of mental health professionals** is limiting the number of patients who can be assessed and prescribed mental health interventions. A report by the National Audit Office NHS highlighted that retaining mental healthcare professionals is becoming an increasing challenge: during 2021–22, 17,000 staff (12%) left the NHS mental health workforce, up from 13,000 (9%) a year earlier.[74] According to a report released by the US Department of Health and Human Services Health Resources and Services Administration, the field of mental health will be 250,000 professionals short of the demand projected for the year 2025.[75] The Mental Health Atlas estimated there are 1.6 mental health workers per 100,000 people across Africa, compared to the global average of 13 workers per 100,000 people.[76] In most African countries, the number of available psychiatrists is less than the recommended 1 to 10,000 population ratio.[77]

7.4 Inequalities

There is a cycle of inequality present within the mental health R&D ecosystem. **Inequalities** that exist already feed into the development of new interventions and in turn, this further widens inequalities. For example, higher stigmatisation among certain sociocultural groups, or increased vulnerability of those with more severe mental health conditions reduces their treatment-seeking and/or enrolment in trials. Trial populations do not therefore represent them and consequently, the interventions developed are not always as suitable for them as other groups. Many of the barriers described, for example, stigma, non-representative trials, digital divide and affordability are also felt more strongly in low- and middle-income country settings. Barriers that either stem from or widen inequalities are highlighted with red borders in Figure 20, which presents an overview of the barriers in the mental health R&D ecosystem identified in this study, illustrating their interlinked nature.

8 Prioritisation of the barriers

As a part of the study, a virtual prioritisation workshop was held to build consensus around identified barriers that are top priorities for the stakeholders. The format of the exercise was as follows: Prior to the workshop, representatives from multiple stakeholder groups, including developers, funders/investors, policymakers/regulators, and people with lived experience (PWLE), were asked to rank the top barriers across each of the major themes: **high development cost**, **the complex regulatory and policy environment**, and the mental health treatment **market seen as unattractive**. During the workshop, the study team presented the gathered evidence and led a discussion on findings. Participants were then asked to re-rank the barriers, and shifts in priorities were noted.

8.1 High development costs

Due to the large number of barriers associated with high development costs, participants were requested to prioritise the top five barriers in this category.

Prior to the workshop, participants collectively identified the high dropout rate in clinical trials and the lack of biomarkers as the primary barriers of concern. This was followed by the lack of flexibility in RCT design, prolonged timelines for clinical trials, and the challenge of translating trial results into real-world evidence.

The discussions underscored several challenges in conducting clinical trials. A technical barrier is the detection of molecular target engagement, i.e. measuring binding of the molecule being tested to target proteins in intact cells. Reliance on RCT methodology was also highlighted as challenging, with small companies often struggling to cover the costs. Participants advocated for real-world evidence studies as a valuable alternative. Additional concerns relating to clinical trials included delays in obtaining ethical approval and unique challenges in developing interventions for children and young people. In the latter context, cost-effective approaches such as psychoeducation are weighed against evidence-based interventions, especially in cases where young people exhibit lower trust in practitioners. Furthermore, sustaining engagement from children and young people is challenging.

The participants also discussed opportunities for reducing the high costs associated with developing new interventions. Digital approaches and AI were proposed as potential solutions; however, concerns were raised that these could reduce the human connection in patient-clinician interactions. Moreover, the importance of involving people with lived experience (PWLE) in the development process was emphasised, highlighting a potential gap in developer mindset, as PWLE are often eager to contribute but may not be adequately consulted.

After the discussion and ‘re-voting’, the order of barriers in the prioritisation ranking shifted. ‘Poor recruitment and retention in trials’ emerged as the most important barrier, despite not having ranked among the top five previously.

The challenge of trial findings not translating to real-world scenarios shifted from fifth place to second in the ranking. The final prioritisation of barriers related to high development costs is presented in Table 21.

Table 21 Final list of prioritised barriers relating to high development costs

Priorities	Barrier	Brief description
1	Challenging recruitment and retention of participants clinical trials	Mental health pharmaceuticals face challenges in recruitment hurdles, leading to difficulties in obtaining the required sample size, contribute to trial failures. Health providers may hold preconceived ideas about patients' suitability for participation, potentially reducing enrolment. Additionally, caregivers may harbour concerns about supporting individuals through lengthy trials, further complicating the recruitment process. Patient dropouts also present a challenge for conducting clinical trials in mental health. Participants can withdraw if they suspect they are on a placebo or not receiving active treatment, especially evident in trials involving psychedelic drugs. Vulnerability to mental health deterioration heightens the risk of participant dropout during trials focused on mental health interventions. Additionally, decreased motivation, a common feature of many mental health conditions, poses challenges in maintaining participant engagement and regular attendance at assessments.
2	Trial results do not translate to real-world scenarios	Clinical trials for mental health interventions face challenges in translating anticipated treatment effects to real-world scenarios, primarily due to the clinical heterogeneity within mental health conditions. Diagnostic categories encompass diverse symptoms, comorbidities, and underlying mechanisms, leading to varied responses within patient subgroups. Demographic underrepresentation in clinical trials, particularly of marginalised groups and racial/ethnic minorities, limits the generalisability of findings. Strict exclusion criteria further contribute to non-representative populations, excluding individuals with more severe conditions. Difficulty in recruiting marginalised and minority populations, coupled with a lack of culturally and linguistically appropriate health staff, compounds the issue, hindering diverse trial recruitment and impacting the applicability of trial data to real-world settings.
3	Gaps in scientific knowledge	Diagnosis and treatment of mental health conditions primarily rely on symptomatology rather than standardised chemical or molecular markers. While certain genes and protein expressions are associated with specific conditions, no standard diagnostic markers exist, partly due to the costly development of biomarkers. The complex links between molecular mechanisms and mental health symptoms pose significant challenges, impacting the understanding of how existing pharmaceuticals and medical devices achieve therapeutic effects. The lack of scientific understanding in mental health means that conducting hypothesis-driven clinical trials is challenging. The higher perceived risk of failure for developers narrows the opportunities to conduct clinical trials.

8.2 Complex regulatory and policy environment for market access

Prior to the workshop, participants were asked to rank the top three barriers relating to the complex regulatory system. 'Time and resources required to navigate regulations' emerged as the most significant barrier, followed by 'variability in pricing and reimbursement models', and regulations not being suited for innovative or digital therapeutics.

During the discussion, participants highlighted that developers of digital mental health interventions often decide to target the unregulated consumer and wellness market, thus avoiding the lengthy and costly regulatory pathway. This raises concerns over the effectiveness of products. Stakeholders cited NICE's Early Value Assessment[117] and the DiGA framework[118] as good initiatives to accelerate the development of digital mental health apps but the developers mentioned that they still have high evidence requirements and could benefit from being less stringent.

The re-assessment of barriers after the workshop discussion saw the order of the top two barriers reversed, with variability in pricing and reimbursement models ranked in first place, followed by 'time and resources required to navigate regulations'. Both barriers are associated with regulatory uncertainty. The final prioritisation of barriers related to the complex regulatory system is presented in Table 22.

Table 22 Final list of prioritised barriers relating to the complex regulatory system

Priorities	Barrier	Brief description
1	Variability and complexity of the pricing and reimbursement models	Pricing and reimbursement processes are varied and not adapted well for digital therapeutics and preventing these solutions to be deployed and taken up in health systems.
2	Regulatory uncertainty related to the time and resources required to obtain marketing authorisation.	Navigating regulations for mental health interventions proves time-consuming and resource-intensive, generating uncertainty in timelines, resources, and requirements, causing investment concerns. The complexity and regional variations of regulations, coupled with the unconventional nature of innovative mental health technologies, pose challenges for developers. Non-pharmaceutical developers may struggle with self-certified risk-based approaches, and therapeutic products, especially those based on psychedelics, face licensing issues. The lack of clarity often results in products taking incorrect regulatory pathways.
3	Regulation is not suited for innovative or digital therapeutics	Digital developers avoid costly and complex regulatory pathways to develop therapeutics targeting clinically diagnosed mental health conditions and instead opt to develop wellbeing apps for the unregulated market. Innovative approaches (e.g. psychedelics) are not suited for current regulatory environment.

8.3 Unattractive regulated mental health treatment market

Prior to the workshop, participants were asked to indicate the top four barriers that contribute to developers' view of the mental health treatment market as unattractive. A shortage of mental health professionals and the unaffordability of mental health treatments emerged as the two primary barriers. This was followed by 'low treatment seeking due to stigma, fear, or perception of not needing treatments', 'proliferation of digital well-being products without sufficient evidence of effectiveness', and 'challenges in adapting interventions to user's cultural background'.

During the workshop discussion, participants highlighted several reasons for why the mental health interventions market can be considered unattractive by investors and end users. These included:

- Access issues, including the digital divide and language accessibility
- A lack of mental health services in certain countries, especially in LMICs
- Low uptake of treatment by patients due to side effects of pharmaceutical interventions and poor patient adherence

Stakeholders noted pharmaceutical companies' limited interest in developing mental health drugs due to perceived difficulty and high trial costs.

Participants highlighted issues relating to health systems more broadly, such as the need for improved digital records and the ability for remote patient monitoring.

Barriers to uptake included a shortage of healthcare professionals, inadequate communication of treatment options to patients, lack of awareness among PWLE about clinical trial opportunities, stigma, and affordability concerns, particularly in low- and middle-income countries (LMICs).

After the discussion, workshop participants ranked stigma around accessing mental health interventions at the top of the list of barriers. The final prioritisation of the barriers related to the complex regulatory system is presented in Table 23.

Table 23 Final list of prioritised barriers relating to unattractive regulated mental health market

Priorities	Barrier	Brief description
1	Low treatment seeking by patients due to stigma, fear, or perception of not needing treatment (treatment gap – demand side challenges)	Access to mental health treatment is particularly challenging for individuals in LMIC and ethnic and racial minorities, as well as marginalised populations such as prisoners, those experiencing homelessness, individuals with drug addiction, and those in extreme poverty. A substantial portion of individuals with mental health challenges do not actively seek treatment, limiting the market size and return on investment for mental health treatments. Factors contributing to underutilisation include perceived lack of need, negative beliefs, fear of treatment (e.g. concerns about memory loss), and uncertainty about treatment consequences. Stigma, especially prevalent in low-resource areas and among vulnerable populations, further hinders health-seeking behaviour within the healthcare system and among professionals.
2	Access to patients due to shortage of prescribing health professionals (treatment gap – supply/demand side challenges)	Health professionals are 'gatekeepers' for supplying prescription mental health interventions. However, shortage of trained primary care professionals and mental health professionals limit patient assessment and eventual prescription of mental health solutions, limiting the number of patients who can benefit from mental health interventions. (This issue also affects clinical trial recruitment)
3	Alternative direct market access route for digital well-being products without sufficient evidence of effectiveness	There is a proliferation of wellbeing apps claiming to improve elements of mental health and few of them are supported by robust evidence of efficacy. This makes patients' choice extremely difficult and without guarantees of positive health outcomes.

9 Potential solutions

The previous sections demonstrated the complexity of the barriers prevailing in the mental health R&D ecosystem. The many causes and stakeholders involved in the R&D ecosystem highlight the need for the community to come together to address these issues.

This section explores mental health initiatives that are currently in place to help address some of the barriers identified, potential gaps that are still to be filled, and present potential solutions for consideration. The solutions focus on addressing the prioritised barriers. For the full literature review on the potential solutions to remaining barriers, see Appendix D. We have identified approximately 30 mental health initiatives in the context of the priority barriers in the mental health R&D ecosystem. We also comment, where applicable, on any results and (early) impacts of these initiatives, as well as the extent to which they have successfully reduced or mitigated issues concerning the barriers in the mental health R&D ecosystem, see Appendix N.

It is important to note that this list is not exhaustive, it is intended to provide a snapshot of the current and larger initiatives implemented around the world. As such, there may be other initiatives with a more general approach to addressing mental health and mental well-being that have not been included here. The recommended actions for investors and funders to fill the gaps that remain addressing barriers are provided in Section 10.

9.1 The mental health initiatives landscape

Initiatives designed to improve mental health and well-being encompass a broad range of activities, many of which aim to address aspects of the mental health R&D ecosystem. These initiatives, typically driven by non-profit organisations, governments and/or other advocacy groups, can help to promote mental well-being, prevent mental health disorders, and improve access to mental health care. Common objectives and associated activities of mental health initiatives include:

- **Raising awareness** to encourage open discussions about mental health and reduce the stigma associated with mental health disorders. This, in turn, can have a positive effect on individuals' treatment-seeking behaviour or enrolment in clinical trials.
- **Prevention and early intervention** in the form of educational programmes or community outreach activities can help individuals recognise and address mental health concerns before they escalate. Initiatives of this type have commonly been aimed at children and adolescents; and at adults by addressing well-being in the workplace.
- **Advancing research and innovation** in mental health is usually done through funding calls and providing grants to sponsor

research programmes aiming to enhance the understanding of mental health conditions and their causes in order to improve treatment and implement research-based and innovative interventions. These initiatives are typically sponsored by non-governmental organisations (NGOs) and/or public bodies. More recently, however, venture capitalists, greatly driven by a growing market since the onset of the COVID-19 pandemic, have been reportedly investing substantial amounts in mental health start-ups.[119] Venture capitalists, such as *What If Ventures,*[120] *InHealth Ventures,*[121] or *Telosity Ventures*[122] are actively investing in start-ups working on developing mental health digital services or interventions such as telehealth solutions or mobile applications. An analysis by *Sifted* reports that venture capitalists have invested £1.7bn into mental health start-ups between 2020 and the end of 2022.[123] The mental health research propelled by these types of initiatives are often carried out by a consortium of academic and non-academic actors, and (small) private enterprises.

- **Training and capacity-building** initiatives for health professionals, practitioners, and social care workers, among others, can help to address a shortage of mental health professionals. Training programmes, guidance, and toolkits can aid (primary care) professionals in diagnosing mental health disorders and prescribing the most efficient and appropriate intervention.
- **Improving access to affordable and quality mental health care services** such as therapy, psychiatric care, or counselling can have a positive impact on patients seeking and receiving the right kind of treatment for mental health disorders. Initiatives of this type are often, but not exclusively, aimed at LMICs where mental health service capacity is scarce. These initiatives can also play a role in promoting the use of digital therapeutics and mobile applications for individuals with limited or difficult access to health facilities.
- **Advocacy for policy change** at a local (e.g. community or regional), national, or even global level can enact improved mental health legislation and policies. These can help to integrate mental health into the overall healthcare systems and/or persuade greater public spending to fund mental health research, for example.
- **Community support** programmes can help individuals and families cope with mental health challenges. These include helplines, forums, and educational material, among others.

These objectives are by no means mutually exclusive, and it is common for an initiative to address, at least indirectly, several of these. For instance, raising awareness of mental health conditions can help to advocate policy change, which itself can have a positive effect on advancing research and innovation in mental health or in

improving access to mental health services.

Table 24 provides a mapping of a selection of current initiatives and the key barriers these are aimed to address in the mental health R&D ecosystem. We will delve into more details on the initiatives and the barriers they address in the following sections, including the global initiatives and a series of initiatives being driven by organisations in the United Kingdom, United States, and the European Union, as well as a small subset of initiatives taking place in Africa.

The mental health initiatives landscape primarily focuses on addressing what is commonly viewed as an 'unattractive' market, largely due to low treatment-seeking rates influenced by stigma and a shortage of mental health professionals. While several initiatives strive to simplify navigating regulatory complexity, notable gaps persist, especially regarding pricing and reimbursement practices. Despite attempts to tackle some of these barriers, there remains a significant gap in addressing the substantial costs associated with mental health intervention development. This discrepancy emphasises the necessity for comprehensive strategies that not only streamline regulatory processes but also address the financial barriers hindering the development and accessibility of mental health interventions. One area that appears to be lacking is the need for active engagement with people with lived experience (PWLE) in both the development and regulatory stages. Therefore, in the following sections, we highlight potential solutions that could specifically address these gaps.

Table 24 Organisations providing initiatives mapped to priority barriers

Initiatives	High development costs			Complex regulations and market access			Unattractive regulated market		
	Challenging recruitment and retention of participants in clinical trials	Trial results do not translate to real-world evidence	Gaps in scientific knowledge	Variability and complexity of the pricing and reimbursement models	Regulatory uncertainty related to the time and resources required to obtain marketing authorisation	Regulation is not suited for innovative or digital therapeutics	Low treatment seeking by patients	Access to patients due to shortage of prescribing health professionals	Alternative direct market access route for digital well-being products
World Health Organization									
World Economic Forum									
United for Global Mental Health									
National Institute for Health and Care Research (UK)									
UK Research and Innovation									
MQ Mental Health (UK)									
Wolfson Foundation MH Initiative (UK)									
Psychiatry Consortium (UK)									
National Institute for Health and Care Excellence (UK)									
Medicines and Healthcare products Regulatory Agency (UK)									
National Institute of Mental Health (US)									
One Mind (US)									
Clinical Trial Transformation Initiative (US)									
Foundation for the National Institutes of Health (USA)									
European Commission									
Accelerating Clinical Trials in the EU Initiative									
European Alliance Against Depression									

Initiatives	High development costs			Complex regulations and market access			Unattractive regulated market		
	Challenging recruitment and retention of participants in clinical trials	Trial results do not translate to real-world evidence	Gaps in scientific knowledge	Variability and complexity of the pricing and reimbursement models	Regulatory uncertainty related to the time and resources required to obtain marketing authorisation	Regulation is not suited for innovative or digital therapeutics	Low treatment seeking by patients	Access to patients due to shortage of prescribing health professionals	Alternative direct market access route for digital well-being products
German Federal Ministry of Education and Research									
Innovative Health Initiative/Innovative Medicines Initiative (Europe)									
African Mental Health Research Initiative									
Centre for MH Research and Initiative (Nigeria)									
South African Federation for Mental Health									
South African Medical Research Council									

Source: Technopolis. *Key: Darker shading indicates that the initiative addresses the priority barrier directly.*

9.2 Potential solutions for addressing the high development costs

Barriers contributing to the high development costs identified as important to be addressed are as follows:

- Challenging recruitment and retention of participants in clinical trials
- Gaps in scientific knowledge
- Trial results do not translate to real-world scenarios

9.2.1 Implementation of strategies to support participant recruitment and retention

Our research confirmed that developers find it challenging to recruit people to clinical trials for mental health interventions, which affects trial success rates. The resulting additional costs and uncertainty feed forward and cause developers to prioritise other therapeutic areas, reducing the flow of innovative treatments for mental health conditions. Recruitment to clinical trials is particularly difficult because of (i) the heterogeneity of the large numbers of people living with different mental health conditions and the need for bigger samples, (ii) concerns amongst healthcare professionals and carers about the appropriateness of recommending clinical trials to people that may be vulnerable and possibly even have challenges with their decision-making capacity, and (iii) a negative feedback loop whereby historically low levels of mental health research and clinical trials means there are many groups and areas that have been under-served and where there is less capacity and infrastructure to promote and support the recruitment of people to trials.

Active engagement with participants and stakeholder groups, including researchers, caregivers, and patients throughout the clinical trial process is crucial.[124,125] It is essential for researchers to plan strategies at the design stage, as making changes during the trial may exceed financial and staffing capabilities. Monitoring recruitment rates and assessing the cost-effectiveness of strategies throughout the study are important. Solutions can be categorised based on their applicability to both majority and minority ethnic groups, with some requiring additional resources specifically for ethnic minorities. Formal testing of these strategies is necessary to demonstrate their effectiveness and cost-effectiveness, preferably through nested trials within ongoing clinical trials. Increasing cultural sensitivity in research among ethnic minorities is also important; introducing culturally sensitive recruitment methods without corresponding cultural adaptations in interventions might decrease participation retention.[125]

Furthermore, building active engagement with the practitioner community, attending relevant events, and promoting third-sector organisations to become attuned to the relevant needs and difficulties for patient and practitioner populations have been suggested.[50,124,125] Consideration should also be given to the disruption that participation in trials poses in general, such as the cost of travel to the site, whether participation interferes with work or caring

commitments, or whether it impacts participants' wages.[50,124,125] In addition, acceptability studies with potential participants as part of the trial process are recommended. In one study, this involved semi-structured interviews to identify people willing to participate in a randomised trial.[126] It was highlighted by our expert advisors that addressing dropout rates in RCTs involves recognising two distinct types: early treatment terminations and data dropout. Understanding these dropout patterns can offer valuable insights into treatment effectiveness and areas for potential improvement.

Existing initiatives such as the UK's NIHR Clinical Research Network (CRN) – expected to transition to the Research Delivery Network (RDN) in April 2024 – support clinical research and participant recruitment. In 2019/20, these efforts resulted in 70,767 participants joining 327 mental health studies, with over 80% of non-commercial studies meeting recruitment targets.[127] Additionally, the NIHR Mental Health Research Groups (MHRGs), established in September 2023, foster collaborations between higher education institutions to address mental health challenges in underserved areas.[128] In the US, the Clinical Trial Transformation Initiative (CTTI), co-funded by the FDA and Duke University, tackles issues such as high failure rates and lengthy delays in clinical trials. By uniting stakeholders, including patients, clinicians, sponsors, and regulators, CTTI focuses on designing quality trials, embracing digital health, engaging patients, and ensuring ethical research practices.[129] These initiatives serve as models for addressing recruitment and retention challenges in mental health clinical trials, highlighting the value of global engagement in this area.

Patient involvement in the R&D pathway is essential for improving both retention and recruitment in mental health studies. Recognising the significance of lived experience input, such as in projects like gameChange for VR development (see Appendix G), not only enhances patient participation but also improves intervention development, thereby increasing acceptance among target end users. Emphasising the importance of involving individuals with lived experience at the outset of studies maximises their effectiveness.

There is a growing recognition of the importance of involving people with lived experience (PWLE) in research, and several initiatives have been launched to encourage developers to involve PWLE in the R&D process. For example, MQ's Transforming Mental Health Initiative emphasises data-driven, inclusive, sustainable, and collaborative approaches to R&D. With £23m invested in various research programmes, including support for early career scientists and initiatives like PsyImpact, MQ aims to improve treatments and prevent mental illness.[130] Furthermore, the European Commission's (EC) ENGAGE project (2023–2028, €1.5m) aims to improve digital mental health interventions by collecting information on how users engage and disengage with digital mental health interventions.[131]

In addition, participant education and the enhancement of Informed Consent Forms (ICFs) play pivotal roles in better recruitment. It is important to thoroughly inform and educate participants about the potential burdens of participation in clinical trials (specifically in the context of Deep Brain Stimulation (DBS) device trials,[125] and drug trials).[132] This includes understanding short and long-term risks, travel requirements, psychosocial adjustments, and post-trial care. Avoiding therapeutic misconception is crucial, ensuring that participants are not exposed to risks solely due to misunderstanding. Accessibility and clarity of the information provided, especially in ICFs, are essential to ensure comprehension among non-scientific audiences.[133] For example, poor understanding of placebos may impact retention. Obtaining ICFs from familial caregivers, in addition to direct participants, is recommended for better inclusion and understanding.[50] Overall, efforts to effectively communicate trial details and requirements have led to improved patient satisfaction.[134]

Using medical devices often raises concerns about invasiveness, which can hinder recruitment. Addressing this challenge involves **envisioning future technology designs**, particularly focusing on **improving device-tissue interfaces to reduce invasiveness**. For example, advancements in enabling recharging implantable devices like DBS aim to minimise the need for Implantable Pulse Generator (IPG) surgeries.[76]

Currently, there are no initiatives specifically focused on advancing the development of less invasive medical devices. Existing initiatives primarily concentrate on digital therapeutics and non-invasive wearables designed for tracking lifestyle behavioural changes or indicators for predicting relapses to enhance treatments. These initiatives include the EC's IMMERSE project, which aims to create a clinical digital mental health tool using mobile sensing data and innovative machine learning models for treating mental health disorders.[135] The NEVERMIND project has resulted in an e-health system comprising a wearable smart sensing monitoring device (i.e. a 'smart shirt') connected to a mobile application providing lifestyle behavioural advice to recognise and reduce depressive symptoms among patients diagnosed with severe somatic conditions.[136] The ENGAGE project aims to improve digital mental health interventions by collecting information on how end users engage and disengage with digital mental health interventions, informing the direction of product development.[131] Similarly, the Innovative Medicines Initiative (IMI) RADAR-CNS project aimed to develop new ways of monitoring depressive conditions using wearable devices and smartphone technology to predict the occurrence of relapses and enhance treatments to prevent recurrence.[137]

Finally, **leveraging existing databases** can significantly enhance patient recruitment and clinical trial research in mental health. While partnerships with public infrastructure and public datasets, such as those exemplified by programmes such as Increasing Access to Psychological

Therapies (IAPT) and the large data collected through the NIHR CRN initiative in the UK, showcase the benefits of integrated systems, there are broader opportunities to explore. For instance, the vast dataset gathered by such programmes, encompassing millions of individuals with mental health conditions, remains an underutilised resource due to accessibility constraints. Funding organisations could enhance data curation and accessibility by collaborating with these public infrastructures and datasets, enabling researchers to gain valuable insights for mental health research. However, it is essential to acknowledge that such partnerships may not exist universally, and where they do not, exploring avenues for similar collaborations should be considered. Encouraging collaboration between digital developers and local services, aligned with national procurement systems, can facilitate data linking and sharing, thereby maximising the potential of existing databases for evidence generation and patient recruitment.

Various initiatives are bolstering clinical trials infrastructure and establishing centralised patient databases to advance medical research. The European Commission, in collaboration with the Heads of Medicines Agencies and the European Medicines Agency (EMA), initiated the Accelerating Clinical Trials in the EU (ACT-EU) program, aimed at revolutionising clinical trial practices. Activities include training for the Clinical Trials Information Systems (CTIS), facilitating multinational clinical trials, and establishing a multi-stakeholder platform.[138]

Additionally, the Accelerating Medicines Partnership (AMP),[139] managed by the Foundation for the National Institutes of Health (FNIH),[140] features the AMP Schizophrenia (SCZ) project, launched in 2020. SCZ aims to develop tools for early-stage schizophrenia risk detection, psychosis progression prediction, and identification of new drug targets. Its objectives include validating biomarkers for clinical high-risk (CHR) individuals, building a global research network, enabling CHR individual identification for trials, and disseminating research data through the US National Institute of Mental Health (NIMH) Data Archive platform. Private-sector partners are investing $18.3m over five years, with NIMH contributing $99.4m. As of February 2024, NIMH supports three research projects under AMP SCZ, focusing on biomarker collection, disease progression monitoring, and algorithm development for CHR outcomes prediction.[141,142]

Furthermore, United for Global Mental Health (UnitedGMH) advocates for mental health rights and improved healthcare systems globally, fostering ecosystems through enhanced financing and data quality while amplifying the voices of PWLE.[143] Despite these efforts, gaps persist in fully leveraging existing patient databases and creating a centralised infrastructure for researchers and developers to access.

The potential solutions presented to address the issue of poor recruitment

and retention are currently actioned in part by initiatives in mainly HICs with some at the global level. However, no initiatives identified are currently targeting the mental health R&D ecosystem in LMICs directly, and gaps remain in knowledge sharing and having a joint effort to address this barrier. The recommended actions for investors and funders to fill the gaps that remained in addressing this barrier are outlined in Section 10.

9.2.2 *Supporting the identification of disease mechanisms and biomarkers with targeted funding schemes*

A significant challenge in psychiatric pharmaceutical development is the limited understanding of the underlying disease mechanisms. Despite substantial funding into infrastructure set ups, coordination between stakeholders for expediting early-phase studies remains inadequate, with major pharmaceutical companies showing little interest while smaller firms drive innovative developments. Reconsidering the relationship between industry and academia is imperative, prioritising early patient input, diversity, and study relevance to foster meaningful progress.

Existing initiatives aiming to enhance collaboration between industry and academia include the UK's NIHR Mental Health Translational Research Collaboration (MH-TRC)[144] and the NIHR Biomedical Research Centres (BRC),[145] bringing together leading researchers in the field of mental health from across the UK to accelerate the translation of research findings and lab-based scientific breakthrough into practical applications such as new treatments or diagnostics. The MH-TRC is also in the process of implementing the NIHR's Mental Health Mission (MHM), a substantial £42.7m investment to pioneer innovative interventions and technologies for diagnosing, monitoring, and treating mental health challenges. This funding will establish demonstrator sites, enhance NHS mental health research capacity, and translate research outcomes into clinical practice. Notably, the MHM prioritises overcoming research barriers, fostering new industrial partnerships, and trialling interventions in areas with significant mental health needs, ensuring a sustainable environment for advancing mental health research.[146,147] This initiative is also important in addressing the barrier of clinical trials not translating to real-world settings.

UK Research and Innovation (UKRI), primarily led by the Medical Research Council (MRC), has invested significantly in mental health research. Over the past five years, MRC alone has allocated over £140m to address mental health inquiries.[148] Initiatives under UKRI include funding calls such as 'Adolescence, mental health and developing mind', which aims to explore emergence of mental health conditions in young people and early intervention methods, with a £35m budget spanning from 2019 to 2026.[149] Additionally, the upcoming 'Mental Health Platform Hubs' initiative, starting in April 2024 with £17.5m in total funding, seeks to establish hubs for large-scale research on strategic mental health needs.[150] Moreover,

UKRI has set up eight Mental Health Research Networks to foster collaboration among researchers, charities, and organisations to address critical mental health research questions and promote mental well-being.[151]

The lack of biomarkers for mental health conditions is a pressing scientific barrier to support targeted development efforts and treatment-predictive biomarkers to identify responsive patient subsets. For example, EEG and neuroimaging technologies are suggested for Phase 1 drug trials and pain-related research, which can be an approach adapted for mental health drug development and scientific research. This has the potential to validate biomarkers, requiring large sample sizes and standardised sample processing. Technologies such as whole genome sequencing, proteomics, metabolomics, and digital applications are anticipated to accelerate biomarker validation, with smartphones potentially facilitating data collection for digital biomarkers, representing a significant advancement in mental health research.[65,78,84–86,152,153]

Increased collaboration through joint funding for large-scale, long-term studies and partnerships focusing on disease mechanisms, target identification, and biomarkers could address gaps in scientific knowledge. The literature highlights these gaps in mental health research, prompting calls for further investigation and trials.[76,77,154] Collaboration between academia, and public and private sectors is crucial for advancing basic science, with proposals to accelerate research through the establishment of large, possibly international patient registries to expand data availability.[77,154]

Several initiatives are aimed at addressing the lack of biomarkers and understanding of disease mechanisms in mental health research. The Psychiatry Consortium, managed by the UK's Medicines Discovery Catapult and supported by Wellcome, engages with research institutions globally to investigate genes like KALRN, NEGR1, and GALR3 as potential targets for treating mental health disorders.[155] Similarly, the NIMH Fast-Fail Trials (FAST) Initiative, conducted between 2012 and 2015, enhances early drug development phases by rapidly testing new compounds for potential psychiatric medication use, identifying biomarkers and drug targets for mood and anxiety disorders, and including schizophrenia.[156]

In addition, the One Mind Accelerator supports early-stage start-ups, emphasising biomarkers and diagnostics among its key focus areas to develop innovative solutions for mental illness treatment.[157] Meanwhile, the One Mind AURORA initiative, led by scientists at various US universities and supported by NIMH, aims to enhance understanding, resilience, and recovery among trauma survivors, leveraging physiology, genomics, neuroimaging, and wearable technology.[158]

The FNIH Deeda Blair Research Initiative For Disorders of the Brain accelerates basic research to discover new therapeutic targets for severe mental illnesses, supporting projects

ranging from integrating neuroscience into clinical practice to understanding molecular mechanisms in psychiatric disorders.[159] The Biomarkers Consortium (BC), managed by FNIH, leads efforts to validate and qualify biomarkers for drug development.[160]

Moreover, The Centre for Intervention and Research on Adaptive and Maladaptive Brain Circuits (C-I-R-C), funded by the Federal Ministry of Education and Research (BMBF) in Germany, investigates neural and immune access points underlying behaviour in mental disorders, aiming to provide application-oriented neuroscience insights across all age groups.[161]

These initiatives will certainly aid research by having better collaborative infrastructure and funding opportunities. However, there remains a need for leadership to pave the way for more global initiatives and collaborative efforts in understanding the mental health disease mechanisms and identifying relevant biomarkers. The recommended actions for investors and funders to fill the gaps that remain in addressing this barrier are outlined in Section 10.

9.2.3 Translating clinical trial results to real-world settings

One of the biggest challenges in translating research results from clinical trials to real-world scenarios is related to the diversity of mental health conditions. Individual research studies primarily focus on identifying and addressing psychiatric subtypes, stressing the need to connect subtype identification with specific outcomes or questions.[80,87,162,163] The Biological Classification of Mental Disorders (BeCOME), initiated in 2015 at the Max Planck Institute of Psychiatry in Germany, integrates various data levels to comprehensively phenotype individuals across the depression and anxiety spectrums. Within BeCOME, machine learning supports identifying biologically-informed diagnoses and tailoring individual therapeutic interventions.[162] Moreover, there is a push to explore biological mechanisms such as epigenetic processes, the hypothalamic-pituitary-adrenal (HPA) axis responsiveness, and neurotransmitter imbalances.[80,87] Beyond mental health, in pain research, big data and machine learning also hold promise for developing composite biomarkers and extracting patterns from self-reports of pain using text mining tools.[164] The utilisation of machine learning techniques to pinpoint subtypes of mental health conditions hinges on robust data repositories and potential implementation of the BeCOME study protocol, which offers a fresh approach to subtyping beyond symptom-based classification.[162] These collective efforts strive to confront the challenges posed by the heterogeneity of mental health conditions.

Another related issue is the requirement of implementing strict exclusion criteria in RCTs, which has led to clinical studies that are relevant to only about a fifth of the real-world population living with mental health conditions, potentially excluding those with higher risk or more severe symptoms.[90] There is a growing emphasis on addressing these overlooked populations to meet their

treatment needs. To aid recruitment in challenging trials, it has been proposed that a pre-trial acceptability study assesses the feasibility and acceptability of the proposed intervention or trial among potential participants. Such a study gathers insights into participants' perceptions, preferences, concerns, and anticipated barriers. Despite occasionally overestimating recruitment rates, this approach remains a valuable investment, ensuring trial inclusiveness without compromising the investigation of intervention effectiveness.[165]

Addressing underrepresented populations in trials also involves establishing open data repositories to capture heterogeneities and long-term behavioural changes, with continuous validation of machine learning models.[166,167] Strategies ensuring maximum representation of marginalised groups include translating research tools, culturally adapting information forms, and providing financial and logistical support to developers.[89,168,169] Proactive implementation and continuous monitoring of these strategies are essential, similar to approaches in HIV research aimed at increasing diversity in clinical participation and reducing stigma.[170–173] This underscores the importance of enhancing research focus on underrepresented populations and adopting diverse recruitment strategies to mirror real-world demographics and overcome stigma-related barriers, ultimately improving recruitment to clinical trials and advancing research inclusivity.

Initiatives such as the CTTI are paving the way for the design of higher-quality trials while ensuring ethical standards and inclusivity.[129] On the other hand, IMI PRISM focuses on bridging the gap between the discovery and validation of biomarkers, ensuring that trial findings effectively translate into real-world applications.[174] The NIHR MH-TRC [144] and BRC[145] unite leading UK researchers in mental health to expedite the translation of lab discoveries into real-world treatments and diagnostics. This collaboration is crucial for overcoming the barrier of clinical trials failing to translate into practical applications. Lastly, the Accelerating Medicine Partnership (AMP) is working to ensure the inclusion of clinically high-risk individuals in trials through its AMP Schizophrenia programme.[141,142]

Table 25 maps the potential solutions and examples of existing initiatives to barriers identified.

Table 25 Solutions and initiatives for addressing barriers related to high development costs

Barriers addressed	Potential solutions	Existing Initiatives
Poor recruitment to clinical trials and high participant dropout/low retention	Expand general efforts to raise awareness of and showcase the value of engagement in mental health clinical trials	NIHR: Mental Health Research Groups (MHRGs), Clinical Research Network (CRN) Clinical Trial Transformation Initiative (CTTI)
Poor recruitment to clinical trials and high participant dropout/low retention	Emphasise the importance of involving people with lived experience (PWLE) from the outset of research studies (and throughout the research lifecycle)	EC: PsyPal, ENGAGE MQ Transforming Mental Health Initiative
Poor recruitment to clinical trials and high participant dropout/low retention Gaps in scientific knowledge	Strengthen clinical trials infrastructure and create a centralised patient database (can leverage existing databases)	Accelerating Medicine Partnership Schizophrenia (AMP SCZ): PREDICT NIHR Clinical Research Network (CRN) NIMH Data Archive platform (e.g. statistics on prevalence and treatments) Accelerating Clinical Trials in the EU (ACT-EU) Initiative United for Global Mental Health (UnitedGMH) gateway to MH data
Poor recruitment to clinical trials and high participant dropout/low retention	Improving device-tissue interfaces and future-proof technology designs	N/A
Gaps in scientific knowledge Trial results do not translate to real-world scenarios	Enhanced collaboration between industry and academia by fostering stronger partnerships to prioritise patient input, diversity, and study relevance	NIHR: Mental Health Translational Research Collaboration (MH-TRC) UKRI: Mental Health Research Networks MQ Transforming Mental Health Initiative Psychiatry Consortium One Mind German Centre for Mental Health's Clinical and Medical Scientists Programmes FNIH: Accelerating Medicines Partnership (AMP)

Barriers addressed	Potential solutions	Existing Initiatives
Gaps in scientific knowledge	Allocate resources for developing treatment-predictive biomarkers, utilising EEG, neuroimaging, and digital applications to accelerate validation	One Mind: Accelerator Accelerating Medicines Partnership (AMP) Innovative Medicine Initiative: NEWMEDS, PRISM
Gaps in scientific knowledge	Facilitate joint funding for long-term studies and partnerships, bridging public-private sectors to address scientific gaps and advance mental health research	NIHR: Mental Health Translational Research Collaboration (MH-TRC) UKRI: Mental Health Research Networks MQ Transforming Mental Health Initiative Psychiatry Consortium One Mind German Centre for Mental Health's Clinical and Medical Scientists Programmes FNIH: Accelerating Medicines Partnership (AMP)
Trial results do not translate to real-world scenarios	Develop and implement objective assessment tools that rely less on subjective measures and more on common biological mechanisms to improve the validity and reliability of clinical trial results	IMI: PRISM Clinical Trial Transformation Initiative (CTTI) NIHR: Mental Health Translational Research Collaboration (MH-TRC), Biomedical Research Centres (BRC)
Trial results do not translate to real-world scenarios	Implement strategies to enhance diversity in trial populations, particularly among marginalised groups and racial/ethnic minorities, to improve the generalisability of findings	Clinical Trial Transformation Initiative (CTTI) Accelerating Medicine Partnership (AMP) NIHR: Clinical Research Network (CRN)
Trial results do not translate to real-world scenarios	Review and potentially revise strict exclusion criteria to ensure they do not inadvertently exclude individuals with more severe conditions or from marginalised populations, thus improving the representativeness of trial populations	Clinical Trial Transformation Initiative (CTTI) Accelerating Medicine Partnership (AMP) NIHR: Mental Health Translational Research Collaboration (MH-TRC), Biomedical Research Centres (BRC)

9.3 Potential solutions for addressing complex regulations and market access

The following barriers address the issue of a (perceived) complex regulatory and market access system, adversely affecting the development of mental health interventions:

- Variability and complexity of the pricing and reimbursement models (for digital therapeutics specifically)
- Regulatory uncertainty related to the time and resources required to obtain marketing authorisation
- Regulation is not suited for innovative or digital therapeutics

9.3.1 Improving the pricing and reimbursement models for digital therapeutics

To address the complexities of pricing and reimbursement models in healthcare, leveraging existing value-based assessment frameworks and incorporating the perspectives of people with lived experience (PWLE) in decision-making processes is essential.[175] Regulatory uncertainty for developers is a significant barrier to progress, compounded by variations in regulatory frameworks across different regions. Existing initiatives such as the World Economic Forum's (WEF) Global Governance Toolkit for Digital Mental Health: Building Trust in Disruptive Technology for Mental Health and the UK's National Institutes for Health and Care Excellence (NICE) Early Valuation Assessments (EVAs) were launched to provide value-based assessment frameworks and guide pricing and reimbursement for digital therapeutics.

The WEF's Global Governance Toolkit for Digital Mental Health provides a policy framework for governments and regulators to enhance the role of technology in mental health, intending to improve accessibility, quality, and safety of services. A crucial aspect is the seamless integration of digital tools into health systems, which involves addressing pricing and reimbursement of services specific to the countries where the tools are implemented. Notably, New Zealand's Ministry of Health piloted the toolkit during the development of the Digital Mental Health and Addiction Services Evaluation Framework. However, the impact of these initiatives is yet to be evaluated.[176]

NICE has developed the Early Value Assessments (EVAs) for MedTech,[177] enabling rapid evaluations of digital products, devices, and diagnostics regarding clinical effectiveness and cost-effectiveness. These assessments encompass a range of areas, from digitally enabled therapies for adults with anxiety[178] and depression[179] to virtual reality technologies for certain forms of psychosis,[180] and self-help digital cognitive-behavioural therapy for children and young people experiencing anxiety symptoms.[181] NICE provides recommendations for cost-effective digital therapeutics, but the ultimate decision on implementation lies with the NHS. However, concerns persist among digital therapeutics developers regarding the barriers posed by pricing, reimbursement, and integration challenges within the NHS. Since NICE's EVAs is an early assessment,

developers have the opportunity for adjustment before the final evaluation, but it does not directly address the pricing and reimbursement issues.

Fast-track regulatory approvals such as the NICE EVAs and Germany's DiGA have allowed digital therapeutics to reach the market more quickly. However, this approach has led to sustainability issues, necessitating a re-evaluation of evidence for pricing and reimbursement.[182] Real-world data holds promise in informing technology development and enhancing regulatory vigilance, with potential alignment with regulatory bodies such as the MHRA.

Moreover, addressing the challenge of defining inclusion and exclusion criteria for digital start-ups is crucial, with insights from the FDA's utilisation of real-world data in the US offering valuable guidance.[183] Overall, adopting a strategy that harmonises the diverse regulatory approaches and incorporates real-world evidence can contribute to a better pricing and reimbursement system for developers.

Therefore, despite the existing initiatives aiming to address the barrier of pricing and reimbursement of mental health solutions, further work is needed to ensure the pricing and reimbursement framework in different country settings are attractive to developers and allow for return on investment. The recommended actions for investors and funders to fill the gaps that remain in addressing this barrier are outlined in Section 10.

9.3.2 Harmonisation and streamlining the regulatory process for digital therapeutics

To enhance the regulatory pathway, particularly for emerging digital therapeutics, there is a need to define and streamline the process.[100] While fast-track initiatives have eased some challenges, integrating real-world data to tackle placebo issues in RCTs could further alleviate barriers associated with navigating the regulatory pathways, saving considerable time and resources.[184] Moreover, fostering greater harmonisation among regulatory systems across different countries would enhance clarity and coherence.[182] Similar to pricing and reimbursement decisions, incorporating the perspectives of PWLE in decision-making processes is critical. Convening international regulators to deliberate on future regulatory models holds promise for enhancing patient outcomes and advancing healthcare globally.

Several initiatives are underway to harmonise and streamline regulatory processes, incorporating the perspectives of PWLE. Globally, the WEF's Global Governance Toolkit for Digital Mental Health aims to establish ethical standards and promote their global adoption.[176] In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) partnered with NICE, receiving £1.8m from Wellcome in October 2022 to explore and develop guidance on regulating digital mental health products.[185] This collaboration engages stakeholders, including PWLE, experts, and international partners, with anticipated outcomes including the publication of

guidance documents to clarify regulations.[186] Similarly, the Psychiatry Consortium's primary objective is to fund and support mental health research that involves various stakeholders, including PWLE, committing £4m to deliver early-phase drug discovery projects. This funding opportunity, open globally, provides access to expertise and support for project management.[187] Additionally, the ACT-EU initiative seeks to establish a multi-stakeholder platform to aid in the adoption of revised EU guidelines for clinical trial design and provide guidance on decentralised clinical trials, further supporting developers and leveraging available training activities in Clinical Trial Regulation.[138]

These initiatives aim to support developers to navigate the regulatory system with less time and resources, and aid in the engagement of PWLE in decision-making. However, there remains the need for key funders to bring about international standards and engage with PWLE during the regulatory approval process. The recommended actions for investors and funders to consider helping further the efforts already at play are outlined in Section 10.

9.3.3 *Incentivise innovation through wider policy changes to become future-proof*

The proliferation of unregulated digital therapeutics marketed as wellness applications underscores the need for clarity regarding the regulatory status and evidentiary standards. Establishing a comprehensive, publicly accessible repository containing transparent information on ownership, launch date, durability, and version history can empower patients and clinicians to make informed decisions. To enhance the rigour of digital app development, partnerships between academic researchers and health technology companies can enhance quality control in an unregulated market.[188] Integrating evidence-based digital interventions into healthcare delivery services, such as prescription availability, can further improve engagement with these interventions.[189] Recognising the transformative potential of digital interventions, as demonstrated in the case studies on digital therapeutics (Appendix, G, Appendix H, and Appendix I), underscores the importance of embracing these technologies in modern healthcare practices. Furthermore, proposing wider legislative changes, such as the decriminalisation of psychedelics for medical research, can foster innovation in alternative treatment options.

Currently, several initiatives are addressing the challenge posed by regulations that are not suited for innovative or digital therapeutics by establishing clear regulatory standards for these interventions to differentiate them from wellness apps. Wellcome-funded work by MHRA, in collaboration with NICE, is exploring and developing guidance on regulating digital mental health products. This effort aims to publish guidance that provides a clear evaluation of mental health digital therapeutics, aiding patients, the public, and healthcare professionals in making informed decisions about the best digital therapeutic options.[186]

Additionally, the NIHR Policy Research Unit (PRU) is advancing mental health intervention policy through funding research initiatives, fostering collaborative partnerships, advocating for supportive policies, and generating evidence-based recommendations. These endeavours seek to drive innovation in mental health interventions, ensuring alignment with policy objectives and real-world needs, thereby facilitating their integration into healthcare systems.[190] Furthermore, the WEF's Global Governance Toolkit for Digital Mental Health not only aims to assist end users in understanding the potential of digital mental health but also seeks to improve access and effectiveness of digital therapeutics by integrating digital tools into healthcare systems.[176]

A potential solution is to establish a comprehensive, publicly accessible database to provide details on digital therapeutics, helping for health professionals and patients to make informed decisions. The One Mind PsyberGuide, established in 2013, serves as a platform offering unbiased expert reviews of mental health apps and digital health resources,[191] yet there remains a barrier preventing end users and healthcare providers from making fully informed decisions, indicating the need for further work in this area. Additionally, broader legislative changes, such as decriminalising psychedelics for medical research, have the potential to foster innovation in alternative treatment options. The European Commission's PsyPal project (2024–2027, approx. €6.5m) will explore the clinical effects of individualised and patient-centred psilocybin therapy, potentially paving the way for wider legislative changes and encouraging innovation in alternative mental health treatments.[192] This showcases regulators' willingness to explore alternative treatments, and efforts should be made to expand this globally, particularly in countries where psychedelics are still considered dangerous substances. Finally, facilitating collaborations between academia and digital therapeutics developers can help enforce rigorous quality standards in app development.

Table 26 maps the potential solutions and examples of existing initiatives to barriers identified.

Table 26 Potential solutions and initiatives for addressing barriers related to the complex regulations and market access

Barriers addressed	Potential solutions	Existing Initiatives
Variability and complexity of the pricing and reimbursement models (for digital therapeutics)	In-depth analysis into HTA processes of mental health technologies and clear and transparent pricing and reimbursement processes for digital therapeutics	NICE: EVA WEF: Global Governance Toolkit for Digital Mental Health
Variability and complexity of the pricing and reimbursement models (for digital therapeutics) Regulatory uncertainty related to the time and resources required to obtain marketing authorisation	Involve PWLE in decision-making	MHRA: project to explore and produce guidance on regulation digital mental health tools (together with NICE, and funded by Wellcome) Psychiatry Consortium NICE: EVA
Variability and complexity of the pricing and reimbursement models (for digital therapeutics specifically) Regulation is not suited for innovative or digital therapeutics	Leveraging real-world data to inform technology assessment	MHRA: project to explore and produce guidance on regulation digital mental health tools (together with NICE, and funded by Wellcome) NICE: EVA
Regulatory uncertainty related to the time and resources required to obtain marketing authorisation	Streamline the regulatory process and guidelines	MHRA: project to explore and produce guidance on regulation digital mental health tools (together with NICE, and funded by Wellcome NICE: EVA EC: ACT-EU
Regulatory uncertainty related to the time and resources required to obtain marketing authorisation	Harmonisation among regulatory systems across different countries	WEF: Global Governance Toolkit for Digital Mental Health
Regulation is not suited for innovative or digital therapeutics	Define clear regulatory standards for digital therapeutics to distinguish them from wellness apps	WEF: Global Governance Toolkit for Digital Mental Health NIHR Policy Research Unit in Mental Health MHRA: project to explore and produce guidance on regulation digital mental health tools (together with NICE, and funded by Wellcome)

Barriers addressed	Potential solutions	Existing Initiatives
Regulation is not suited for innovative or digital therapeutics	Encourage integration of evidence-based digital interventions into healthcare services to enhance patient engagement	WEF: Global Governance Toolkit for Digital Mental Health
Regulation is not suited for innovative or digital therapeutics	Establish a comprehensive, publicly accessible database providing transparent details on digital therapeutics to empower informed decisions	One Mind PsyberGuide
Regulation is not suited for innovative or digital therapeutics	Propose wider legislative changes, such as the decriminalisation of psychedelics for medical research, to foster innovation in alternative treatment options	EC: PsyPal
Regulation is not suited for innovative or digital therapeutics	Facilitate collaborations between academia and tech companies to enforce rigorous quality standards in app development	N/A

9.4 Potential solutions for addressing the unattractive regulated mental health treatment market

The following barriers address the issue of a (perceived) unattractive treatment market, affecting the development of mental health interventions:

- Low treatment seeking by patients due to stigma, fear, or perception of not needing treatment
- Access to patients due to shortage of prescribing health professionals
- Alternative direct market access route for digital well-being products without sufficient evidence of effectiveness

The mental health sector, despite its critical importance in global healthcare, often faces significant challenges that render it less attractive to investors and developers. Unlike some other areas of healthcare, the mental health market grapples with a unique set of barriers that impede its growth and development. These barriers, ranging from societal stigma to regulatory challenges, leading to low return on investment (ROI), and creating a landscape where investment and innovation are deterred, hindering progress in addressing mental health needs effectively.

Our study identified key solutions to address barriers in the mental health market. One significant challenge is the treatment gap resulting from low treatment-seeking behaviour among patients, often due to stigma, fear, or a perceived lack of need for treatment.

To tackle this, awareness campaigns emphasising the benefits of treatment and incorporating cultural sensitivity could help build trust and encourage patients to seek help. Another barrier is the shortage of mental health professionals, which can widen the treatment gap. Implementing digital therapeutics and providing training to healthcare professionals could increase the availability of mental health support and alleviate the workload on existing professionals. Additionally, the digital divide contributes to low user engagement, hindering access to mental health resources. Measures such as enhancing digital literacy, improving accessibility across cultural and language barriers, providing free devices through a donation scheme, and increasing internet access can potentially bridge this gap, ensuring equitable access to suitable treatment options, whether digital or non-digital.[115,193]

There is a growing effort in addressing these barriers. As seen in Table 24, there is a large number of initiatives globally aiming to increase the attractiveness of the mental health market, focusing on addressing issues related to stigma and fear leading to low treatment seeking patients, and building mental health professional capacities. The impact of these initiatives is yet to be evaluated.

Initiatives addressing these barriers at the global level include the World Health Organization (WHO) championing global mental health advancement through initiatives like the Special Initiative for Mental Health, aiming to extend care to 100 million people across 12 countries, scaling up quality services in community-based and general health settings,[194] and the Mental Health Gap Action Programme, which supports non-specialist health workers with intervention guides.[195] Furthermore, United for Global Mental Health (UnitedGMH) advocates for mental health worldwide, securing funding, supporting suicide decriminalisation, and amplifying patient voices.[143]

In the UK, initiatives such MQ's 'PsyImpact' programme aim to improve treatment access, while the NIHR Incubator for Mental Health Research strengthens research capacity and promotes career opportunities.[196] In the US, the NIMH conducts crucial research, trains scientists, and communicates mental health priorities.[197] Meanwhile, the non-profit organisation One Mind champions positive attitudes through its One Mind PsyberGuide, providing impartial expert reviews of mental health apps and digital resources.[191] In Europe, the European Commission's Comprehensive Approach to Mental Health initiative dedicates €1.23bn to address mental health challenges, reinforcing systems and expanding treatment access.[198] Additionally, the European Alliance Against Depression, a community-based multi-level intervention programme comprising training for General Practitioners, public awareness campaigns, training of community facilitators, and support for patients and their relatives. [199] Furthermore, the German Centre for Mental Health fosters interdisciplinary collaborations, with a key focus on enhancing the appeal of mental health

research careers through its 'Clinical and Medical Scientists Programmes'.[200]

Notably, while initiatives targeting development costs and regulatory challenges often overlook LMICs, several initiatives are actively addressing the unattractive treatment market in LMICs. Firstly, the African Mental Health Research Initiative (AMARI) primarily focuses on capacity building for mental, neurological, and substance use research in Ethiopia, Malawi, South Africa, and Zimbabwe. The initiative targets fellows in MPhil, PhD, and post-doctorate programmes, offering intensive training to secure their future in research. AMARI is part of the Wellcome's DELTAS programme in Africa.[201] Additionally, the Centre for Mental Health Research and Initiative (CEMHRI) is a non-profit organisation in Nigeria dedicated to promoting mental health awareness and eradicating associated stigma. CEMHRI aims to become a leading centre of excellence in Africa, providing information, research, data, and services in mental and neurological health. Its objectives include organising seminars and workshops to raise awareness, disseminate information, and build the capacity of health workers and the general population in preventing, managing, and coping with mental illness.[202] Lastly, the South African Federation for Mental Health (SAFMH) is dedicated to promoting mental health and well-being in South Africa. Focusing on advocating for the rights of individuals with psychosocial disabilities, SAFMH actively raises awareness, reduces stigma, and supports policies that enhance mental health services and inclusion.[203]

Finally, there is an opportunity for investors and funders to provide funding for the creation of a trend tracker database, similar to the G-FINDER[204] (Global Funding of Innovation for Neglected Diseases), which annually tracks global investments into neglected disease R&D, offering insights into funding trends and priorities.[205] Adopting a similar framework for the mental health market could provide valuable data on investment patterns and areas of need, guiding resource allocation and policy decisions to address mental health challenges effectively.

Table 27 maps the potential solutions and examples of existing initiatives to barriers identified.

Table 27 Potential solutions and initiatives for addressing barriers related to the unattractive regulated mental health treatment market

Barriers addressed	Potential solutions	Existing Initiatives
Low treatment seeking by patients due to stigma, fear, or perception of not needing treatment	Awareness campaigns emphasising the benefits of treatment and incorporating cultural sensitivity	United for Global Mental Health (UnitedGMH) Centre for Mental Health Research and Initiative (CEMHRI) South African Federation for Mental Health (SAFMH)
Access to patients due to shortage of prescribing health professionals	Providing training to healthcare professionals about digital therapeutics	WHO: Special Initiative for Mental Health Mental Health Gap Action Programme NIHR Incubator for Mental Health Research European Alliance Against Depression German Centre for Mental Health: Clinical and Medical Scientists Programmes African Mental Health Research Initiative (AMARI)
Alternative direct market access route for digital well-being products without sufficient evidence of effectiveness	Creating a trend tracker database to help investment decision-making	One Mind PsyberGuide

10 Conclusions and Recommendations

The mental health R&D pathway from research to early adoption of solutions has a number of key challenges identified and described in this study. The pathway, developers need to take, represents a 'leaky research pipeline', suffering from attrition at various stages. In this section, we review the key barriers along this pathway and suggest actions for consideration for research funders and investors with (potential) interest in the mental health area. We focus on the following three actionable areas when formulating our recommendations:

- **Funding** to encourage and enable innovation through financial support for educational activities, research programmes, and infrastructure development to drive innovation and accessibility in mental health research.
- **Convening** to catalyse collaborations by bringing stakeholders together to launch campaigns, workshops, and regulatory discussions, fostering collaboration and best practice sharing.
- **Advocating/influencing** to drive change in the research funding landscape, policy and regulatory context of mental health interventions, and for the meaningful involvement of individuals with lived experience.

1. Gaps in basic scientific knowledge about the biological mechanism of action of mental health conditions and the lack of suitable animal models make hypothesis-driven traditional experimentation challenging, especially for pharmaceuticals. Researchers and developers may decide not to target mental health conditions and enter the technology development pathway. The following actions (in synergy) could unblock this barrier in the longer term:

- Fund large-scale interdisciplinary research programmes to attract talent to the field and tackle the complex scientific challenges underpinning mental health conditions to understand the disease aetiology.
- Convene global multi-stakeholder meetings (including academia, industry, health professionals, PWLE, policymakers and others) to develop a strategic research agenda and corresponding funding mechanism, similar to the EU Joint Programming Initiative or Innovative Health Initiative partnership model, to focus on addressing the gaps in scientific knowledge in mental health research.
- Advocate an increase in global research funding into mental health research to match the share of its disease burden.
- Fund a mental health R&D funds tracking portal (similar to G-FINDER), enabling comprehensive monitoring of investment trends and priorities, harmonisation of research agendas and funding programmes, and optimal resource allocation and policy decisions.

2. Challenging participant recruitment and retention in clinical studies further exacerbates clinical research in mental health. The root causes are stigma, fear and negative perceptions in a vulnerable participant cohort, among others, contributing to developers' perception of the high risk of obtaining the required sample sizes. Research funders, investors and other stakeholders could consider the following actions:

- Fund research initiatives that develop linked datasets, tools and methods for better identification of subtypes of mental health conditions, including predictive analytics and objective assessment tools (e.g. BeCOME).
- Fund to grow a global Lived Experience Network (such as the MQ LEE Network) to create local champions that developers can engage with and who can support participant recruitment to trials.
- Advocate the importance of mental health research in the broader population through engagement with mental health charities and networks of PWLE, through targeted information campaigns to enhance awareness and interest in participating in mental health research.
- Advocate enhanced informed consent forms used in mental health trials that are clear, comprehensive, and culturally sensitive to improve participant understanding and willingness to participate.

3. Trials results do not translate to real-world scenarios for various reasons, e.g. due to the efficacy of interventions under trial conditions do not match effectiveness in the home environment, clinical heterogeneity of mental health conditions, marginalised groups are not involved in clinical trials. Consequently, there can be multiple lines of action to ensure that future mental health interventions produce positive outcomes.

- Fund the development and use of innovative trial methodologies that may be more relevant for mental health research. These could include adaptive, pragmatic, and decentralised trials, collecting digital data and digital endpoints, etc. Ensure that real-world data is accepted as evidence by regulators (see below).
- Fund large-scale demonstrators to provide a platform for digital therapeutics developers to test, validate, and optimise emerging technologies and systems at scales relevant to eventual deployment. This will allow optimisation to maximise real-world effects.
- Fund trials that ensure the inclusion of people historically underrepresented in mental health trials to ensure equity of health outcomes of the interventions developed. This may involve diversity enhancement strategies in clinical trial recruitment and a critical review of exclusion criteria in trial protocols by Research Ethics Committees.
- Advocate research led by people with lived experience to empower

them and ensure research reflects their perspectives (and thereby also fostering trust and rapport with potential study participants, see recruitment challenges above).

- Advocate involving people with lived experience in the selection of outcome measures, ensuring those align with the experiences of the target population and reflect end users' priorities and perspectives on their health-related quality of life.

4. Regulatory uncertainty related to obtaining marketing authorisation poses a significant challenge, especially for innovative approaches and digital therapeutics. The study has shown that regulatory science and practice are not always able to accept novel data and evidence generated by developers, and in some drug types, such as psychedelics, there are legal and regulatory hurdles to obtaining marketing authorisation. The following actions may be taken by research funders to help to address the issue:

- Convene international forums or conferences to foster collaboration and knowledge-sharing among regulators, aiming for more efficient and globally aligned regulatory frameworks on areas of relevance for mental health interventions.
- Convene meetings focused on controversial interventions, such as psychedelics, and facilitate discussions to address regulatory obstacles effectively.
- Advocate mental health to be recognised as an unmet medical need globally and unblock regulatory incentives to accelerate development to marketing authorisation for mental health technologies.

5. The variability and complexity of pricing and reimbursement models across global markets pose significant challenges. Fragmented national rules around cost-effectiveness assessment and health system recommendations vary greatly, adversely affecting developers' decisions about the attractiveness of regulated markets. This makes scaling up products regionally a costly endeavour, especially for smaller developers of digital therapeutics. Research funders and investors may consider the following actions:

- Convene international forums to foster collaboration and knowledge-sharing among HTA bodies, aiming for more efficient and globally aligned scientific frameworks on areas of relevance for mental health interventions and specifically for digital therapeutics.
- Advocate the involvement of PWLE in decision-making on the most effective mental health products to ensure their perspectives are considered in assessments.
- Fund clinical comparative effectiveness studies, specifically for SMEs, to develop evidence for submission to HTA and P&R bodies. Note that this financial support to SME cost may encourage digital therapeutics developers to enter the regulated health market (rather than the well-being market, see below).

6. The alternative direct market access route for digital well-being products opens a new, faster and less costly route for developers of mental health products (often without sufficient evidence of effectiveness). The lack of evidence can create confusion for patients to choose the right product, the associated (out of pocket) cost may become a barrier to access for marginalised groups, and health professionals are unable to prescribe these well-being products. Research funders may use their power and influence to help tackle this problem by considering the following actions:

- Convene focus group discussions with industry on enforcing quality control measures and establishing rigorous standards for mental health intervention development.
- Fund a bespoke prize for developers of popular digital apps on the well-being market to demonstrate the effectiveness of their solutions and, on positive outcomes, facilitate deployment and uptake of their product in the national health system.
- Advocate easier deployment and uptake of mental health interventions in the health systems.

7. Low treatment-seeking by patients driven by stigma, fear, or perception of not needing treatment, creates a significant 'treatment gap'. This gap represents demand-side challenges for developers, as the estimated large market size does not translate into real demand. This issue is particularly acute for marginalised groups and populations in LMICs.

Moreover, this barrier is closely linked to the challenges of participant recruitment and retention in clinical studies, suggesting that similar actions may be considered to address both issues:

- Advocate awareness programmes and information campaigns in target populations through engagement with mental health charities and networks of PWLE about the importance of recognising and seeking treatment for mental health conditions.

8. Access to patients is limited due to a shortage of prescribing health professionals. The challenge of patients not presenting may be further exacerbated by health professionals not prescribing available treatments for patients, and thus the treatment gap further widens. This may be due to a lack of sufficient training in mental health for primary care providers, awareness about optimal solutions or lack of credible evidence available to them. In any case, in the regulated markets a shortage of 'gatekeepers' also means lower apparent demand for new therapies by patients. This barrier also impacts participant recruitment for clinical trials. Research funders may have limited options to unblock this barrier but could consider the following:

- Advocate more education programmes for primary care providers about mental health and available treatment options.
- Advocate the integration of evidence-based digital interventions into healthcare delivery systems, highlighting their potential benefits

in improving mental health outcomes.

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Appendix A Literature review search terms and sources

A.1. Grey literature sources:

Type of organisation	Name of organisation
Mental health organisations	Active Minds; American Foundation for Suicide Prevention; American Psychiatric Association; American Psychological Association; Anxiety and Depression Association of America; Anxiety UK; Autism Society of America; Beyond Blue; Bipolar UK Ltd; Black Dog Institute; Brain & Behavior Research Foundation; Campaign Against Living Miserably; Centre for Mental Health; Depression and Bipolar Support Alliance; European College of Neuropsychopharmacology (ECNP); Europe; FDA; Headspace; Health Foundation; International OCD Foundation; Mental Health America; Mental Health Foundation; Mental Health Innovations; Mind; National Alliance on Mental Illness; National Association of Anorexia Nervosa and Associated Disorders; National Center for Transgender Equality; National Eating Disorders Association; National Health Service; National Institute of Mental Health (NIMH); NHS; NHSX; OCD Action; Pan American Health Organization; Project HEAL; Rethink Mental Illness; SANE; Spring Care; Inc.; Substance Abuse and Mental Health Services Administration; The Banyan; The Jed Foundation; The Trevor Project; To Write Love on Her Arms; Together for Mental Wellbeing; Trans Lifeline; Treatment Advocacy Center; World Federation for Mental Health; World Health Organization; YoungMinds
Pharmaceutical companies	AbbVie; Abbvie Inc; Amgen; AstraZeneca; Bayer; Bayer AG; Boehringer Ingelheim; Bristol Myers Squibb; Eli Lilly And Co; Gilead; GSK; Johnson & Johnson; Lilly; Merck & Co; Merck & Co Inc; Novartis; Novartis AG; Novo Nordisk; Pfizer; Roche; Sanofi; Takeda Pharmaceutical Company; Teva Pharmaceutical Industries
Digital and medical device companies	Abbott; Baxter; Baxter International; Boston Scientific; Cardinal Health Inc; Danaher; Edwards Lifesciences; Fresenius; GE HealthCare; Intuitive Surgical; Johnson & Johnson; Masimo; Medtronic plc; Philips; SIEMENS AG; Siemens Healthineers; Smith & Nephew; Stryker Corporation; Teleflex Inc; Terumo Medical Corporation; Zimmer

A.2. Search Terms:

Mental Health Block (Population, Problem)

(Treatment* OR Health* OR Intervention* OR Treatment* OR Therapeutics OR Therap* OR Mental Health* OR Psychosis OR Depression OR Depressive OR Anxiety OR Mental Disorders OR Mental Illness* OR Obsessive-Compulsive Disorder OR Post-Traumatic Stress Disorder OR Bipolar Disorder OR Schizophrenia OR Panic OR Body Dysmorphic Disorder OR Depressive Disorder OR Affective Disorder OR Premenstrual Dysphoric Disorder OR Psychiatr* OR Psychedelic* OR Psychopharmacolog* OR Antipsychotic* OR Neuropsychiatric).ti.

R&D Block (Intervention)

("AI" OR Artificial Intelligence OR App OR Apps OR Biomarkers OR Brain Stimulation OR Diagnostic* OR Digital OR Direct Current Stimulation OR Drug Development OR Drug Discovery OR Drug Treatment* OR Drugs OR Experimental Treatments OR Innovati* OR Intervention* OR Magnetic Stimulation OR Medical Device* OR Medicine* OR MedTech OR Mobile Health Device OR Mobile OR "R&D" OR Smartphone* OR Neurostimulation OR Neurotech OR Neurotechnolog* OR Novel Agents OR Pharmaceutical* OR Pharmacogenetic Testing OR Psychotherap* OR Research OR Technolog* OR Therapeutics OR Therapy OR Therapies OR Treatment* OR Trial OR Trials OR Wearable Devices).ti.

Characteristics/Challenge/ (Outcome)

("Patient and Public Involvement" OR "Public and Patient Involvement" OR Acceptab* OR Access* OR Adaptive Clinical Trials OR Adoption OR Advances OR Advoca* OR Affordab* OR Application OR Approval OR Availability OR Barrier* OR Borderline Effective* OR Borderline Efficacy OR Bottleneck* OR Breakthrough Therap* OR Challeng* OR Characteri* OR Clinical Trial Network* OR Collaborative Research OR Complexit* OR Concern* OR Consideration* OR Conundrum OR Cost* OR Data Privacy OR Data Sharing OR Decision-Making OR Deploy* OR Develop* OR Development OR Diversity OR Donation* OR Enabler* OR Evaluation* OR Facilitator* OR Failure Rate* OR Fast-Track OR Fund* OR Future* OR Health Economics OR Heterogene* OR Implement* OR Incentiv* OR Infrastructure* OR Innovat* OR Intellectual Property OR Interdisciplinary Collaborat* OR Invest* OR Issues OR Knowledge Gap* OR Lessons OR Limited Effective* OR Limited Efficacy OR Longitudinal Studies OR Marginal Effective* OR Marginal Efficacy OR Market Competition OR Marketing OR Minorities OR Multidisciplinary Collaborat* OR Multi-Disciplinary Collaborat* OR New Therapeutic Targets OR Novel Therapeutic Targets OR Open Data OR Open Research OR Open Science OR Opportunity* OR Overcom* OR Oversight* OR Patent Protection OR Engagement OR Involvement OR Patient-Centered Research OR Patient-Centeredness OR Patient-Centred Research OR Patient-Centredness OR Personalised

OR Personalized OR Precision Medicine OR Private-Public Partnership OR Public-Private Partnership* OR Pull Factor* OR Push Factor* OR Recruit* OR Register-Based Studies OR Regulat* OR Reimburs* OR Research Centers OR Research Centres OR Risk* OR Safeguard OR Safety OR Seed Fund* OR Service Delivery Model* OR Solutions OR Stakeholder Involvement OR Stigma* OR Strateg* OR Streamlined Regulatory OR Success Factor* OR Translational Research OR Trends OR Uptake Rate*).ti.

A.3. Targeted search terms

Digital therapeutic *and* mental health and barriers *OR* challenges

Digital therapeutic *and* anxiety *and* barriers *OR* challenges

Digital therapeutic *and* depression *and* barriers *OR* challenges

Digital therapeutic and psychosis and barriers *OR* challenges

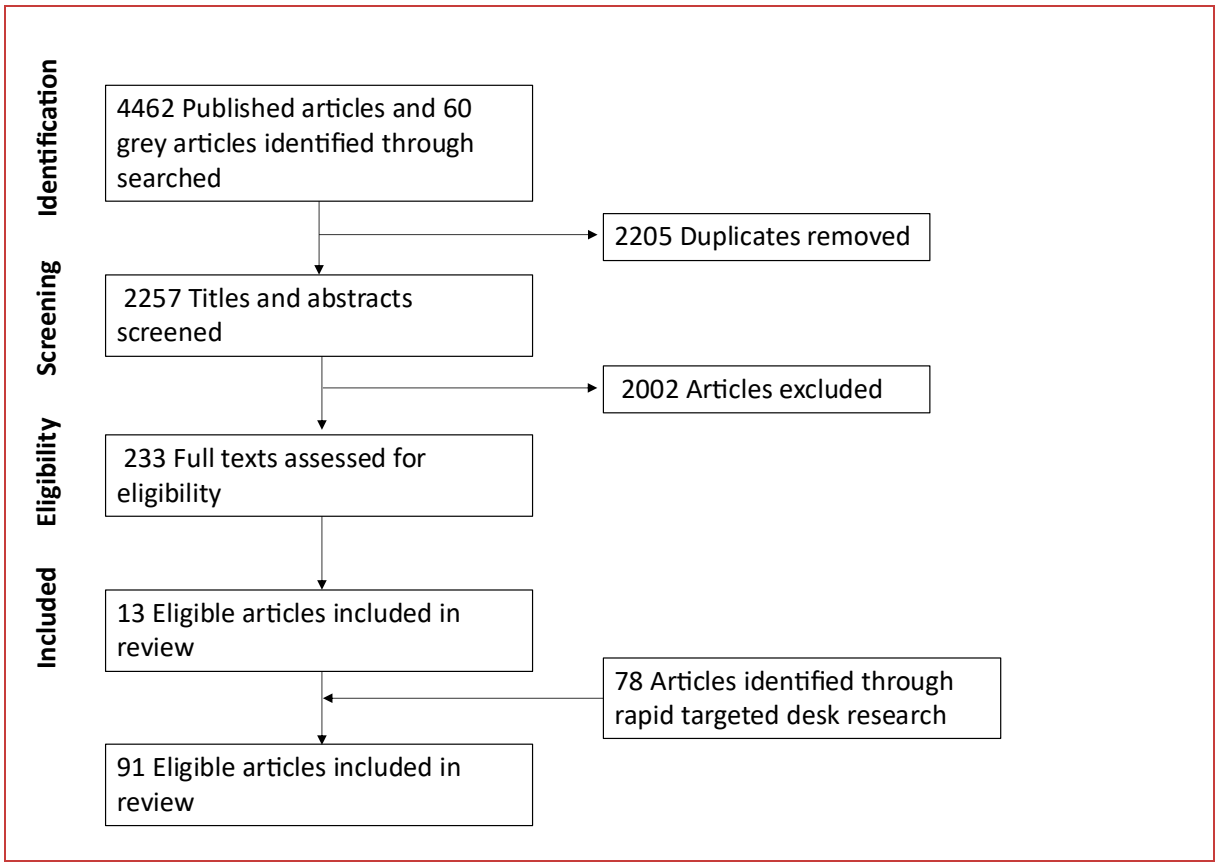
Digital therapeutic *and* mental health *and* barriers *OR* challenges *and* clinical trials

Digital therapeutic *and* anxiety and barriers *OR* challenges *and* clinical trials

Digital therapeutic *and* depression and barriers *OR* challenges *and* clinical trials

Digital therapeutic *and* psychosis and barriers *OR* challenges *and* clinical trials

A.4. Flow diagram for articles that were identified using search terms and strategy



Appendix B Literature review on barriers

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N8	Lack of guidance/real world evidence for decision-makers to select the most effective mental health interventions
N9	Cultural adaption challenges
N10	Mental health inequalities

Challenge number	Scientific challenges		Relevance to mental health intervention type
	Topic	Description	
S1	**Gaps in knowledge of underlying disease mechanisms of mental health conditions**	Despite advances in the field of basic neuroscience **much remains to be understood to establish the links between molecular and cellular mechanisms and mental health symptoms.** Inadequate animal models of mental health conditions are a significant reason for the lack of knowledge on the biological mechanisms contributing to these conditions (challenge: S2). This lack of knowledge of the underlying biological mechanisms of actions at the molecular level contributing to mental health conditions is hindering the identification of novel therapeutic targets, which impedes the development of new pharmaceuticals for people with mental health conditions who are not adequately treated by currently available options.[1–4] Furthermore, the lack of knowledge on the mechanisms by which current pharmaceuticals and medical devices achieve their therapeutic effects is limiting opportunities to develop more targeted mental health therapies.[5,6]	• Pharmaceuticals • Medical devices
S2	**Inadequate animal models to predict side-effects and efficacy of mental health interventions**	**Modelling complex mental health conditions in animals is extremely difficult** due to differences in brain anatomy, neurological pathways and behavioural capabilities between animal models and humans, which is further confounded by the lack of biomarkers (challenge/challenge: S3) to assess emotional and cognitive state in animal models. Without adequate animal models to test mental health interventions there can be a translational gap between preclinical findings and clinical safety and efficacy results, which can lead to clinical trial failures (challenge: N3). [6–12]	• Pharmaceuticals • Medical devices
S3	**Lack of biomarkers to aid the**	The limited knowledge of underlying disease mechanisms of mental health conditions has made it **difficult to identify**	• Pharmaceuticals • Medical devices

	development and testing of mental health interventions	**biomarkers[xxv] that aid the development of more effective and targeted mental health interventions.**[13–15] Although several proteins, metabolites and genes have been linked to certain mental health conditions none of them have proved useful as biomarkers. Another challenge impeding the development of biomarkers is that the validation process is lengthy, expensive and complex.[16,17] The lack of a robust and standardised set of biomarkers for use in routine clinical practice is known to contribute to the limited efficacy of mental health interventions, which can lead to clinical trial failures (see challenge: S7; S8).[7,18]	• Digital therapeutics
S4	**Lengthy timelines and high failure rates of clinical trials for mental health interventions compared to other disease areas**	**Clinical development timelines for pharmaceuticals to treat mental health conditions are some of the longest compared to other disease areas**. For example, anticonvulsants, often used to treat bipolar disorder, have an average clinical research period of 8.1 years, antidepressants average 8.5 years, and antipsychotics 8.6 years[2]. This compares to an average clinical development time of 6.5 years for pharmaceuticals across all chronic illnesses. An analysis of 9,985 clinical and regulatory phase transitions in the period of 2006 to 2015 found mental health clinical trials had the lowest overall success rate compared to 14 other disease areas (6.2% vs 9.6%).[19] Given the lengthy and risky development process, many large pharmaceutical companies including Pfizer, Eli Lilly, GlaxoSmithKline and Astra-Zeneca have withdrawn resources	• Pharmaceuticals

[xxv] Biomarkers are defined as an objective, quantifiable characteristics of biological processes, pathogenic processes or responses to an exposure or intervention. Source: Biomarker Working Group F-N. BEST (Biomarkers, Endpoints, and other Tools) Resource. In: Spring S, editor. *BEST (Biomarkers, Endpoints, and other Tools) Resource.* Silver Spring (MD): FDA-NIH (2016).

		from mental health drug discovery and development (challenge: N1).[1] Clinical trial failures can arise due to a diverse range of factors including inadequate predictability of animal models (challenge: S2), lack of biomarkers (challenge: S3) as discussed above or problems with patient recruitment (challenge: S5) and retention (challenge: S6) as well as clinical design challenges (challenge: S7-S11) as discussed below. Other general factors include lack of funding to complete a trial, failing to maintain good manufacturing protocols and follow regulatory guidance.[20]	
S5	**Clinical trial recruitment challenges**	Clinical trials require the participation of a specific number of participants over the duration of the trial. Inadequate recruitment of patients may lead to trials being delayed, terminated or failing as they are statistically 'underpowered' to validate the clinical hypothesis. **Recruitment of individuals experiencing mental health conditions to clinical trials can be particularly challenging as they may be reluctant to seek mental health care** or accept diagnosis and participate in clinical trials (challenge: N4).[21] A common concern is whether patients possess the mental capacity to provide voluntary informed consent and if it is appropriate for a substitute decision-maker (e.g. legal guardian, spouse, parent) to provide consent for a patient who is deemed not capable to make such a decision.[22,23] **Recruitment barriers can relate to attitudes and perceptions of clinicians and carers** who are involved in the clinical trial recruitment process. Clinicians may have the view that some patients are too unwell to participate in clinical trials or have preconceptions about the outcomes of different mental health interventions and preference for one over the other.[24]	• Pharmaceuticals • Medical devices • Digital therapeutics

		Carers may have concerns about patients being upset by the nature of the research and the high burden on their time to support patients during lengthy clinical trials.[24] With regards to clinical trials of mental health devices, the invasive nature of some medical devices may deter potential participants from enrolling into trials.[25] **Historically, participants in mental health clinical studies have not been demographically representative of the population of people with mental health conditions**. Insufficient consideration of diversity not only hampers the generalisability of clinical studies but also leaves unaddressed the specific needs and concerns of more vulnerable or marginalised groups, which contributes to further widening of health inequalities (Challenge: N10). Racial and ethnic minorities are often not underrepresented in mental health clinical studies.[26] A systematic review of the representation of various sample demographic characteristics in clinical trials for depression over a 36-year period found that racial and ethnic groups are underreported and linguistic minority groups are often largely not represented.[27] A systematic review of barriers to the recruitment of ethnic minority participants into mental health clinical trials reported stigma related to being 'labelled mentally ill' may be a comparative greater deterrent in ethnic minorities compared to the general population.[28] Other barriers associated with recruiting ethnic minorities into mental health clinical studies relate to health service and research process barriers, which included lack of culturally and linguistically appropriate healthcare staff involved in the recruitment process and lack of culturally aware researchers.	

		Furthermore, **stringent eligibility criteria can result in exclusion of some patients** with mental health conditions from clinical trials (e.g. due to the severity of their illness such as tendency to have suicidal thoughts), which can limit real-world applicability of trial results. For example, in the case of patients with schizophrenia only one in five are eligible to participate in clinical trials.[29] The stringent eligibility criteria can be particularly challenging for conducting clinical studies with mental health medical devices that typically target people with serious mental health conditions.[30]	
S6	**Clinical trial retention challenges**	Once patients are recruited to clinical trials there are multiple factors that can lead to patients dropping out/not being retained for the duration of the trial. Poor retention of patients can lead to delays as extensions are needed to recruit more patients or failures as sufficient statistical evidence cannot be obtained to test and validate the clinical hypothesis. **Factors associated with patient drop-out in clinical trials of mental health pharmaceuticals are diverse**, including high study burden which can be especially challenging for mental health patients with significant functional or cognitive impairments that may limit their ability to regularly attend assessments, experiencing adverse side effects, deterioration of mental health, and the absence or challenge to maintain 'blinding'[xxvi] during the clinical trial leading to participants dropping out if they perceive they are not receiving the active treatment.[31,32]	• Pharmaceuticals • Medical devices • Digital therapeutics

[xxvi] Blinding in clinical trials refers to when patients do not know if they have been assigned to the treatment arm of the study (i.e. received active drug) or the control arm (i.e. received non-active drug/placebo)

		Retaining patient engagement and adherence with mental health digital therapeutics in clinical trials is particularly challenging. Even the most well-designed clinical trials of mental health digital therapeutics can have 20-50% of participants drop-out.[33] Low engagement is not unique to mental health digital therapeutics, however, given that decreased motivation is a core feature of many mental health conditions, engagement is even more challenging.[34] A systematic review of over 200 studies investigating user engagement with mental health digital therapeutics found that engagement is influenced by a range of factors including demographic and sociocultural characteristics of individuals, perception of the relevance, usability and credibility of the evidence base informing the digital content, privacy concerns and level of participant digital literacy.[35] Other studies have identified a **lack of co-production between the developers of digital therapeutics,** end users, researchers and clinicians during the design phase to develop digital therapeutics that are tailored to the needs of people with mental health conditions is a reason for low engagement.[36–39] This co-production requires a shift in traditional practice of expert-led development to a practice where digital therapeutics are designed with all the relevant stakeholders. However, there is limited guidance and literature on how this co-production can be done optimally.[40] In addition, a **lack of standardised reporting on engagement metrics** (e.g. rate of intervention uptake, weekly use patterns, and number of intervention completers) is hindering the design of improved engagement and retention strategies.[41]	

S7	**Clinical trial design challenges**	**Subjective nature of mental health assessment**: The assessment of mental health conditions relies on clinically validated but often subjective mental health questionnaires and scales (e.g. Patient Health questionnaire [PHQ] or Generalised Anxiety Disorder Assessment [GAD]). As these assessments are subjective in nature and rely on patient self-reporting and clinician judgement this can introduce variability leading to inconclusive results and clinical trial failures.[2] This is in part owing to the lack of validated biomarkers to objectively assess mental health conditions (challenge: S3).	• Pharmaceuticals • Medical devices • Digital therapeutics
S8		**Clinical heterogeneity of mental health conditions:** Contrary to other health conditions that are classified by common molecular mechanisms of action, mental health conditions are classified by diagnostic categories (e.g. International Classification of Diseases [ICD] or Diagnostic and Statistical Manual of Mental Disorders [DSM]) with a broad variety of clinical symptoms, comorbidity and underlying mechanisms.[42,43] Consequently, subgroups of patients within a mental health condition may respond differently to the same mental health intervention, which can lead to inconsistent clinical trial results that do not accurately represent how treatments will work in real-world settings (i.e. treatments that are shown to be effective in the clinical population sampled may be ineffective or toxic to a subgroup population in the real world). This is in part owing to the lack of validated biomarkers to stratify mental health conditions into subgroups for more targeted treatment (challenge: S3).	• Pharmaceuticals • Medical devices • Digital therapeutics
S9		**Failure to establish an appropriate placebo**: Randomised placebo-controlled trials are considered gold-standard for clinical trials. A placebo is a treatment that has no therapeutic effect which is used to create a control group	• Pharmaceuticals • Medical devices

		against which an active treatment is compared. However, if the placebo treatment is not appropriately designed it can compromise the validity and reliability of the clinical trial results, potentially leading to trial failure. Designing a placebo is particularly problematic for clinical trials of psychedelic drugs to treat mental health conditions due to their unique subjective effects, which results in higher chances of participants realising they have been assigned to the control group that can lead to increased drop-out rates.[44,45] For clinical trials of mental health digital therapeutics it is often not feasible or possible to design an adequate placebo as they are complex in their design.[46,47] For instance, it can be difficult to understand the exact mechanism that produces the therapeutic effect as digital therapeutics can integrate many features such as disease/symptom tracking, behaviour tracking, goal setting, community support, disease related psychoeducation or general lifestyle and wellness content. Therefore, it is challenging to construct a plausible placebo by excluding or altering the main features to leave only the auxiliary function. Consequently, less stringent minimal controls or even waitlist controls are used that may overestimate the therapeutic effect of a digital therapeutic. Designing a placebo for mental health devices can also be challenging. Typically a 'sham' placebo control is designed which is an ineffective device designed to mimic active device stimulation. However, sham stimulation is found to be not entirely equivalent to the treatment condition.[48,49]	• Digital therapeutics
S10		**High placebo effect,** or the improvement of symptoms in response to a placebo can reduce the observed treatment effect, which can make it challenging or impossible to detect	• Pharmaceuticals

		significant differences between the active treatment and placebo, which can lead to clinical trial failures. Clinical trials of mental health pharmaceuticals have been associated with high placebo effect.[50,51] A study in 2022 showed that the placebo effect could be as large as 70-90% in mood disorders and 50-60% for schizophrenia.[52] Factors associated with larger placebo effects include inclusion of patients with lower baseline symptom severity to the control group and 'expectation bias' of participants who have positive expectations that the treatment received may be beneficial.	
S11		**Lack of flexibility of standard clinical trial design methodology** can cause delays or clinical trial failures. Standard randomised control trials require mental health digital therapeutics to be fixed at the trial outset, preventing iterations of the design that may render the technology outdated or obsolete at the end of the trial[Error! Bookmark not defined.]. In the case of mental health medical devices, extensive testing of stimulation parameters is needed which can be a complex and time-consuming process leading to significant delays.[53]	• Digital therapeutic • Medical devices
S12		**Need for multiple trial recruitment sites:** Clinical trials for mental health interventions are typically conducted across multiple sites to allow timely recruitment of sufficiently large samples of patients. However, the inclusion of more sites can lead to inconsistencies in trial procedure compliance and greater patient diversity within a mental health subgroup, which can lead to inconsistencies and unreliable of results.[50]	• Pharmaceuticals
	Non-scientific challenges		
N1	**Insufficient investment in mental health R&D**	There is a **lack of investment in mental health R&D compared to other health areas** despite mental health having a higher burden of disease:	• Pharmaceuticals • Medical devices • Digital therapeutics

		• A study analysing global mental health research funding data (2015-2019) found mental health research represented around 4% of registered grants and 4% of the total research investment (USD 18.5 billion).[54] Most investment in mental health was from high-income countries (89%), with 11% coming from low- and middle-income countries (LMICs) based funders. Grants were predominately for basic research (56%) and categories related to prevention, detection, testing and development of mental health interventions accounted for 24%. • An Analysis of UK Research funding in 2018 found around 6% of the UK's health research budget was spent on mental health[55] and funding level has remained largely unchanged for a decade.[56] • A report published in 2022 found that the National Institutes of Health (NIH), one of the largest US funders for research, level of funding invested into research on serious mental illness is disproportionately low compared to other disease areas. Furthermore, the large majority of funding was allocated to conduct basic research.[2] The insufficient level of investment in mental health R&D hinders the development of novel or improved interventions to treat mental health conditions. A report by the Pharmaceutical Research and Manufacturers of America (PhRMA) reported that, as of January 2023, only 160 pharmaceuticals were in the clinical development pipeline to treat mental health conditions in contrast to more than 1,300 pharmaceuticals in development to treat cancer conditions and 400 to treat infectious diseases.[57]	
N2	**Complex and evolving regulations**	Navigating through complex and evolving regulations and meeting their requirements can be time-consuming and resource intensive, particularly for innovative mental health	• Pharmaceuticals • Medical devices

		technologies and treatment approaches that do not neatly fit into existing regulatory categories. This is further complicated by regulatory frameworks varying between countries and regions. Complex regulatory frameworks can create uncertainty discouraging the investment in mental health interventions (challenge: N3). In the mental health R&D ecosystem, with regards to digital therapeutics, the presence of a consumer 'wellbeing market' and a regulated healthcare market for clinically diagnosed mental health conditions has posed regulatory challenges where developers can apply a self-certified risk-based approach to determine the need for regulation.[58,59] In these cases, a lack of clarity as to where categorical boundaries lie (i.e. between the definition of wellbeing and a 'clinical' mental health condition) can lead to digital therapeutics not going down the most appropriate regulatory pathway. As a result **many developers have opted to invest in the development of unregulated direct-to-consumer wellbeing apps instead of digital therapeutics targeting clinically diagnosed mental health conditions,** which require expensive clinical trials to demonstrate their safety and efficacy. The proliferation of well-being apps claiming to improve various aspects of mental health compared to evidence-based digital therapeutics targeting mental health conditions is a concern in the field.[60,61] A systematic review of over 1000 publicly available wellbeing apps reported only 2% have peer-reviewed research evidence to demonstrate efficacy (challenge: N8).[62] **Many developers of medical devices to treat mental health conditions struggle to understand the regulatory system, with negative impacts on investment decisions** (i.e. how to meet regulatory expectations, how long it will take to approve a	

		new device, and how likely it is to be approved and how much will the entire process likely to cost), which is discouraging investment in this sector.[30]	
N3	**Uncertainty about the return on investment for mental health interventions**	The low return on investment (ROI) for mental health pharmaceuticals compared to other health areas has discouraged industry investment into pharmaceuticals to treat mental health conditions. Challenges include: • **Inadequate patent protection:** The current patent protection and exclusivity periods for approved mental health pharmaceuticals are not considered long enough by industry to offset the higher costs and lengthier R&D timelines for mental health pharmaceuticals (challenge: S4).[2] • **Limited market size for mental health interventions**: Despite the high prevalence of mental health conditions, only a relatively low proportion of people seek treatment. This limits the potential market size and ROI of mental health treatments.[2] It is estimated that 40% of patients living with schizophrenia, 50% of patients living with bipolar disorder, and 35% of patients living with major depression do not seek treatment.[2] The World Mental Health Surveys, conducted in 24 countries with over 6000 responses, found that lack of perceived need for treatment was by far the most frequently reported reason given for not seeking treatment for mental health problems.[63] A recent publication reported a key reason why people fail to seek mental health treatment is because they 'interpret their psychological and emotional states as reactions to social and economic problems, not as health conditions' that can be addressed by mental health interventions.[64] The low demand for mental health treatment also in part stems from	• Pharmaceuticals • Digital therapeutics

		stigma associated with mental health conditions (challenge: N4). • **Therapeutic adherence challenges**: Non-adherence to mental health interventions is recognised as a common problem, which limits the potential market size and ROI. Evidence suggests that the rates of non-adherence for patients taking antidepressants can vary from 10-60%.[65] A multitude of factors can influence adherence to mental health pharmaceuticals such as patients' social and demographic characteristics, education level, cultural context, negative attitudes toward medication, treatment side effects, lack of medication routines, fear of addiction, poor patient and clinician interaction, and unsupportive social networks.[66] **In the case of digital therapeutics, navigating pricing and reimbursement processes is particularly challenging.** Different requirements in different countries impedes their widespread implementation in healthcare systems.[67] • Europe: In European countries, there is no single harmonised pricing and reimbursement process.[67] Germany is the most advanced European country which has implemented the Digital Supply Act (DVG) in 2019, enabling health care practitioners to prescribe digital therapeutics through Statutory Health Insurance (SHI). To accelerate digital therapeutics being made available to patients, Germany was the first country to introduce a new "DiGA fast-track" pathway to accelerate reimbursement through selected SHIs. • US: Public and private providers have different approaches to reimbursement. Private payers are more likely to cover	

		payments for digital therapeutics, while Medicare, one of the biggest public healthcare providers, does not have a reimbursement mechanism for digital therapeutics.[2] The US has recently reintroduced the "Access to Prescription Digital Therapeutics Act of 2023". The bipartisan bill would expand Medicare and Medicaid to include digital therapeutics.[68] • UK: reimbursement occurs at a local level by NHS organisations, with over 40 integrated care systems (ICSs) responsible for digital therapeutic funding. The NHS has identified three criteria that digital therapeutics must meet in order to be reimbursed: (1) obtain CE/ UKCA mark before being placed on the market, (2) fulfil the Digital Technology Assessment Criteria (DTAC) and (3) be recommended by NICE to ensure cost-effectiveness and value for the NHS.[69]	
N4	**Stigmatisation of mental health conditions**	**Stigma associated with mental health conditions is a major factor contributing to the low proportion of patients seeking treatment for mental health conditions.** Stigma appears to be a stronger barrier to mental health treatment access within low-resource areas and among vulnerable members of the population including poor and ethnic minorities (Challenge: N10) .[70,71] Other factors include negative beliefs or fear of treatment (e.g., concerns about memory loss), and misinterpretations or uncertainty about treatment consequences.	• Pharmaceuticals • Medical devices • Digital therapeutics
N5	**Affordability of mental health treatment**	**Some individuals requiring mental health treatments cannot afford the interventions.** Studies from LMICs report that patients are required to pay out-of-pocket for prescribed mental health treatments, which many cannot afford, as they are not available free-of-charge in government pharmacies.[72]	• Pharmaceuticals • Medical devices • Digital therapeutics

		In the United States, the implementation of the Affordable Care Act (ACA) in 2010 has contributed to more individuals being able to afford mental health care. However, 28 million Americans are still lacking any type of health insurance.[73]	
N6	**Shortage of mental health professionals to prescribe mental health interventions and provide therapeutic support**	A challenge to the uptake of mental health interventions is the **shortage of mental healthcare professionals, limiting the number of patients who can be assessed and prescribed mental health interventions:** • A recent report by the National Audit Office NHS highlighted concerns about shortages of mental health medical and nursing staff, and psychologists due to issues with recruiting and retaining staff, a high turnover of staff between service areas, and competition from health and non-health sectors.[74] Retaining mental healthcare professionals was cited as becoming an increasing challenge: during 2021-22, 17,000 staff (12%) left the NHS mental health workforce, up from 13,000 (9%) a year earlier. • According to a report released by the U.S. Department of Health and Human Services Health Resources and Services Administration, the field of mental health will be 250,000 professionals short of the demand projected for the year 2025.[75] • The Mental Health Atlas estimated a figure of 1.6 mental health workers per 100 000 people across Africa, compared to the global average of 13 workers per 100 000 people.[76] In most African countries, the number of available psychiatrists is less than the recommended 1 to 10 000 population ratio.[77] **The shortage of mental healthcare professionals is particularly challenging for the uptake of mental health digital therapies.** Many mental health digital technology	• Pharmaceuticals • Medical devices • Digital therapeutics

		companies have essentially digitised existing behavioural therapies delivered by healthcare professionals. However, studies have shown that a healthcare professional needs to be 'in the loop' to optimise engagement with digital therapeutics.[78] Blended therapies (i.e. combinations of face-to-face sessions with digital sessions) have been shown to increase the acceptability of digital therapeutics for patients. However, healthcare professionals have competing priorities and limited time to support blended approaches. Furthermore, there is a need to train healthcare professionals in the use of digital therapeutics and to develop therapeutic support protocols that are effective and attractive to patients to encourage their uptake.[38]	
N7	**Healthcare professional attitudes and perceptions towards mental health interventions**	**Healthcare professionals can have misconceptions about mental health interventions that can prevent them from being prescribed.** For example, clinicians may have the perception that young people prefer using mental health digital therapeutics despite evidence to the contrary or may not recommend digital therapeutics as they perceive the therapeutic relationship is lost through digitally mediated communication.[79] **Mental-illness-related stigmatisation within the healthcare system and among healthcare professionals has been identified as a barrier to patients receiving treatment**. A systematic review revealed health care professionals in both high-income countries and LMICs can have stigmatising beliefs, attitudes and discriminatory behaviours towards people with mental health conditions.[80] Such stigmatising attitudes undermines access to treatment for people with mental health conditions. Furthermore, it contributes to the reluctance of people to seek help for mental illness.[81,82]	• Pharmaceuticals • Medical devices • Digital therapeutics

N8	**Lack of guidance/ real world evidence for decision-makers to select the most effective mental health interventions**	Healthcare professionals are central to the adoption of mental health interventions given that they are responsible for their prescription and/or influencing their uptake by patients. **Digital therapeutics for treating mental health conditions have shown promising results in clinical trials, however, there is still a lack of rigorous and long-term real-world evidence to support their effectiveness.**[62,83] This can make it difficult for clinicians and patients to make informed decisions about which digital therapeutics to recommend. Studies have reported there is a lack of up-to-date data on the availability of effective and efficacious treatments for mental healthcare in LMICs and how they can be scaled up which is major problem impeding their uptake.[84] Another concern is that **mental health interventions can be prescribed by healthcare professionals who may have limited training in mental health and lack guidance on which interventions would be the most effective to prescribe/ recommend to patients.**[2] A study exploring stakeholder views on practical barriers to the uptake of mental health medical devices revealed concerns about the limited availability of clinicians with expertise to refer and mental health medical devices these interventions.[26] Furthermore, there is a lack of clarity in clinical guidelines on who is an optimal patient and when to start treatment.	• Digital therapeutics • Medical devices
N9	**Cultural adaption challenges**	**A lack of cultural adaptation of mental health interventions to users' cultural backgrounds can impede their acceptance, usability and uptake.** Despite the growth of digital therapeutics for treating mental health conditions in developed countries, there have been only a few examples of adapting them to LMICs.[85] In a systematic review of 55 studies	• Digital therapeutic

		that culturally adapted internet- and mobile-based therapeutics for mental health conditions found there was no association between the extent of adaptation performed and the effectiveness or adherence to digital therapeutics.[86] This highlights the need for more robust evidence and guidelines to better understand how to adapt mental health digital therapeutics to make them more culturally accessible.	
N10	**Mental health inequalities**	**Mental health conditions are closely associated with many forms of inequalities**, with people living with severe mental health conditions being particularly vulnerable. These inequalities are largely driven by complex and interrelated factors, including socioeconomic and demographic factors that can disadvantage certain groups within the mental health population receiving treatment. **People with mental health conditions are less likely to receive treatment in LMICs.** According to a systematic survey of leaders of psychiatry in nearly 60 countries in 2010, the treatment gap – defined as the difference between the number of people that have a mental health condition and those that have access to treatment – is estimated to be as high as 90% in LMICs compared to 50% in high-income countries (HICs).[87] Factors contributing to treatment gap in LMICs included the need for more healthcare professionals to increase access to mental health treatments (challenge: N6), financial challenges due to affordability of treatment where people with mental health conditions in LMIC are less likely to receive treatment, in particular newer and more expensive therapies (challenge: N5) and structural challenges concerning healthcare infrastructure and systems, and policies. **Although prevalence of mental health conditions is not generally higher among racial and ethnic minority groups,**	• Pharmaceuticals • Medical devices • Digital therapeutics

		these groups are often less likely to receive treatment. A report by PhRMA in 2023 reported there have been an estimated 116,722 excess premature mental and behavioural health-related deaths among racial and ethnically minoritised groups and indigenous populations between 2016 and 2020 in the US.[88] Racial and ethnic minorities are 20%–50% less likely to initiate mental health treatment and 40%–80% more likely to drop out of treatment prematurely.[73] growing body of evidence is highlighting populations in LMICs but also in high-income countries who experience exclusion from mainstream society, such as people experiencing homelessness or imprisonment, and those experiencing drug addiction and extreme poverty are more likely to suffer from mental health problems but less likely to receive treatment.[89] **The 'digital divide' is amplifying inequalities** for people with mental health conditions who have limited ability to engage with mental health digital therapeutics either because they do not have access to the internet or the skills to engage with digital content.[90] The digital divide disproportionately affects people with mental health conditions in rural–urban communities as well as people with severe mental health conditions (e.g. bipolar and schizophrenia).[91]	

B.2. Conclusion

The systematic literature review and rapid targeted desk research identified and summarised 12 key scientific challenges and 10 non-scientific challenges. We have indicated which challenge is relevant to which of the different mental health intervention types and have indicated where challenges are interconnected. This list of challenges will be further iterated and expanded on with targeted research throughout the study informed by findings from the interview programme where we are consulting with stakeholders to understand existing challenges that prevent or delay mental health intervention development. Additional challenges identified will be added and researched, challenges will be iteratively organised/(re)categorised and quantified where possible or qualitatively evidenced where not. The literature review on challenges will feed into descriptive summary of R&D ecosystem output which will be a narrative synthesis of the results triangulated from the quantification exercise and the programme of stakeholder interviews.

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Appendix C List of barriers

Barriers and Challenges	
1	**High Development Costs**
1.1	High Clinical Trial Failure Rates
1.11	Poor recruitment to clinical trials
1.111	Perceptions of trial enrollers or carers can reduce enrolment
1.112	Challenges with informed consent for trials
1.113	Devices are often very invasive
1.12	Clinical trials cannot demonstrate effect
1.121	High dropout/low retention in clinical trials
1.1211	Difficulty blinding trials
1.1212	Mental health deterioration during trials, impacting engagement
1.1213	Low motivation as a symptom of mental health conditions
1.122	High placebo effect
1.123	Lack of RCT design flexibility
1.124	Placebo cannot be established
1.125	Inconsistencies in clinical trial data
1.1251	Subjective mental health outcome assessment
1.1252	Multiple trial sites required
1.13	Inadequate animal models
1.14	Lack of biomarkers
1.141	Gaps in scientific knowledge
1.2	Long clinical trial timelines
1.21	Device parameter testing requirements high
1.22	Delays and extensions to trials
1.3	Clinical trial conditions and outcomes do not translate to the real world
1.31	Heterogeneity of mental health conditions
1.32	Clinical trial populations are not representative of the population who will take/use the intervention
1.321	Strict exclusion criteria
1.322	Marginalised groups are less represented in trials
1.3221	Lack of culturally and linguistically appropriate health staff
2	**Regulatory uncertainty**
2.1	Pricing and reimbursement models varied and complex

2.2	Navigating regulation time consuming and resource intensive
2.21	Complex regulations that developers struggle to understand
2.211	Variety of regulatory pathways
2.22	Progression down wrong development pathway
3	**Lack of regulatory/IP incentive**
4	**Inability to patent/protect digital therapeutics**
5	**Developers opt for unregulated wellbeing market**
6	**Developer/Investor concern that the mental health "market" is not attractive**
6.1	Treatment Gap
6.11	Healthcare professional attitudes and perceptions
6.12	Low treatment Seeking
6.121	Perception of not needing treatment
6.122	Fear of treatment
6.123	Stigma of mental health conditions
6.13	Shortage of mental health professionals
6.14	Patient (6.14) and Health Provider (6.15) decision-making challenges
6.141	Lack of real-world data (digital)
6.142	Lack of evidence base (digital)
6.143	Lack of training and guidance for health professionals
6.151	Proliferation of wellbeing apps unevidenced
6.2	Low user engagement (digital)
6.21	Digital divide
6.22	Lack of reporting on and improving engagement strategies
6.23	Cultural adaptation challenges (digital)
6.24	Lack of co-production
6.3	Poor patient adherence (pharma)
6.4	Affordability of mental health treatment

Appendix D Literature review on solutions

Challenge/Barrier		Description of Solution	Relevance to mental health intervention type
High Development Costs			
High Clinical Trial Failure Rates	Poor recruitment to clinical trials	**Strategies to support retention/recruitment** **Active engagement with participant and stakeholder groups.** Authors recommended reducing barriers between researchers, caregivers and patients.[2,3] Active engagement was recommended throughout the trial process,[3] but also more generally. Actions like integration into the practitioner community, attending relevant events and promoting third-sector organisations to become attuned to the relevant needs and difficulties for patient and practitioner populations are recommended. Consideration should also be paid to the disruption that participation in trials poses; the cost of travel to the site, whether participation interferes with work or caring commitments, or whether it impacts participants' wages.[2–4] In addition, acceptability studies with potential participants as part of the trial process are recommended. In one study, this involved semi-structured interviews to identify people willing to participate in a randomised trial.[5] **Participant education and investment in Informed Consent Forms (ICFs).** The core insight from literature underlined the importance of informing and educating participants. Authors highlighted various elements; the importance of ensuring that participants were	• Pharmacological interventions • Medical devices • Digital therapeutics

		thoroughly aware of the potential burden of participation was emphasised (specifically in the context of Deep Brain Stimulation (DBS) device trials,[3] and drug trials[6]). This includes short and long-term risks, travel requirements, psychosocial adjustments, as well as thorough understanding of post-trial care. All of the above is critical to maximise participant retention during the trial[3]. From an ethical stand point, therapeutic misconception should never be the main reason for participants to be exposed to risks.[6] The importance of accessibility of the provided information and ICF are also highlighted to ensure that non-scientific audiences fully understand the content and its implications.[7] For example, poor understanding of placebos may negatively impact retention due to concerns over being placed in the control group.[4] AI is one potential solution in crafting the ICF in a way that is both informative at the correct level as well as compassionate in tone.[4] Efforts to communicate the details and requirements of the trial have resulted in an improved patient satisfaction.[4] Additionally, researchers are recommended to obtain ICFs from familial caregivers as well as direct participants to enable a better inclusion and understanding of what their loved ones agree to undergo.[8] **Devices are often very invasive** Concerns over the invasiveness of medical devices as a challenge to recruitment was approached by envisioning future technology design. In general, the invasiveness of the devices can be reduced by the improvement of device-tissue interfaces.[9] Developments to enable recharging in implantable devices (DBS) in order to minimise Implantable Pulse Generator (IPG) surgeries are also envisioned.[9]	

	Trial does not demonstrate effect	**High placebo effect** The literature approached placebo effect in two distinct ways. One was minimising the number of sites used for trials.[10] Due to the recruitment pressures, trials tend use a large number of sites to maximise the pool of participants. This strategy has, however, been associated with higher heterogeneity and a higher chance of poor quality trial procedure compliance. This, in turn, can lead to poor randomization and blinding, and therefore a higher placebo response,[11] so it is recommended that researchers minimise noise by reducing the used sites to few, high-quality sites.[10] Another approach explored the mechanisms of placebo effects underlying various conditions.[12,13] It is suggested that schizophrenia trials may be less susceptible to the placebo effect than trials concerning depression or anxiety.[12] The potential of the differential emergence of placebo as a cost-effective component should also be explored in the future of mental health practice.[13] Indeed, they called for future research on common and distinct neurological markers of placebo across psychiatric disorders, and their applications in personalised medicine.[13] **Placebo cannot be established** In researching psychedelics, one strategy in avoiding the 'nocebo' effect is to offer a potentially effective, high dose of the psychedelic in question to every patient randomised.[14] This is done to minimise the 'nocebo' effect in comparator arms in clinical trials of psychedelics. An alternative route is proposed via naïve participants by combining active placebo with incomplete disclosure to balance the expectancy effects across treatment arms.[15] In this model, participants would be informed that they receive a range of psilocybin doses and may also receive an active placebo, with full disclosure that the purpose of the active placebo is to reduce their certainty of treatment assignment. The number of study arms (two,	• Pharmacological interventions • Medical devices • Digital therapeutics

		in fact) and the likelihood that their assigned psilocybin dose would be effectively non-therapeutic would not be disclosed.[15] For trialling medical devices, sham conditions are explored for simulating the sensations caused by the treatment.[16,17] The present literature concludes that none of the reviewed sham conditions were sufficiently equivalent to the treatment sensations but voiced hope for the future. Novel stimulation methods, such as high-definition transcranial direct current stimulation (HD-tDCS), combining imaging brain stimulation, and closed-loop brain stimulation, was considered the emerging and existing stimulation techniques, which need to be refined.[16] Determining a placebo for digital interventions can also prove challenging, with many studies lacking clear descriptions of these arms of the trials.[18] Given that these interventions are generally of low risk, minimal controls and waitlist controls are considered sufficient. However, a recommended placebo would be a digital interface that matches the intervention in aesthetics and usability.[19] The addition of a third arm in an RCT was also suggested, for instances where the digital placebo may not be fully inert.[18] The literature also explores the potential of real-world data approaches to address the failure to establish placebo.[20] Digital therapeutics (DTx) are well positioned to collect data, patterns of engagement and/or clinically relevant digital phenotypes of users through software application.[20] Digital applications can be used to evaluate long-term clinical effects which would be challenging to capture in clinical trials.[21] An added value is in the fact that digital endpoints can be collected cost-efficiently in real time. Rare diseases have also considered the potential benefit of real-world data to serve in conjunction with traditional RCTs, which in the field of rare diseases tend to suffer from low participation.[22]	

	Inadequate animal models	**Inadequate animal models** The literature cautions against looking for human-like behavioural patterns in the development of animal models,[23] and indeed look for biological signals, for instance, via predictive validity-enabling screening of potential treatments.[23] This could be done by looking for consistent alterations in animal behaviours in treatments known to be effective in humans.[23] The identification of species-specific behaviours to generalise animal behaviours is another recommended approach.[24] Finally, animal models could be developed to reflect symptoms seen in humans and the variety of ways in which they emerge (i.e., different symptoms within the disorder pool and how they emerge differently from one person to another)[25]. Additionally, the models should mirror biological changes found in the clinical condition, such as alterations in cortisol or corticosterone levels in humans and rodents, respectively.[25]	• Pharmacological interventions
	Lack of biological biomarkers	**Gaps in scientific knowledge** The literature identified several areas benefitting from further research, or trials suffering from present gaps in scientific knowledge. Some called for investigating specific brain areas for the development of novel or enhanced solutions.[9,26,27] These included targeting glutamate and opioid systems and exploring hallucinogen-derived compounds,[27] while others called for further studies on network effects involving the prefrontal cortex and the striatum in the context of DBS.[26] Additionally, calls for translational research were made to understand underlying mechanisms to prompt novel ideas in drug development, citing specifically the recent investment in serotonin 2A receptor antagonists in drug development years after academic research into these compounds.[10] The stance for basic science is	• Pharmacological interventions • Medical devices

		supported by other authors, who call for collaboration between public and private sector as well as academia to this end.[9,28] In terms of methods, proposals are made for large, possibly international patient registries to increase the overall pool of data.[26,27] Such repositories are stated to be valuable for multiple studies and exploratory research,[27] as well as targeting specific effects under observation.[26] **Lack of biomarkers** Several authors call for the investment in biomarker identification. [29–35] For instance, targeted development efforts are urged to subsets of patients who share a homogenous set of disease-specific features to support an effective R&D pathway.[32] Treatment-predictive biomarkers can be used to identify subpopulations most likely to respond to the treatment under investigation.[32] In terms of specific biomarkers, the use of EEG in Phase 1 drug trials is suggested to determine whether the drug under investigation affects brain function to support the decision for proceeding to Phase 2 trials.[29] The use of neuroimaging technology, such as EEG is also used in pain-related research. This is due to their potential for more specificity, especially in terms of different locations and types of pain.[36] Another approach is to direct future research to identify underlying anatomic or genetic factors separating responders from non-responders to Transcranial Magnetic Stimulation (TMS).[30] Such factors could include e.g. the presence vs absence of the brain-derived neurotropic factor genes.[30] It is acknowledged that the validation of biomarkers is a complex process. [33,34] In this process, large sample sizes and the standardisation of sample processing are some of the key recommendations.[33,34] Future technologies are believed to support the expedition of this process via whole genome sequencing,	

		proteomics, metabolomics and brain imaging.[34] In addition, calls are made for the use of digital applications to collect human-smartphone data towards digital biomarkers.[31] The widespread use of smartphones would be a significant enabler in the scaled collection of data towards digital biomarkers.[31]	
Long clinical trial timelines	Device parameter testing requirements high	*[No solutions identified]*	•
	Delays and extensions to trials	Long clinical trial timelines are often a result of a lack of capacity and infrastructure facilitating trial environments and mechanisms. The UK's National Institute for Health and Care Research (NIHR) and the Office for Life Sciences invested £42 million into the Mental Health Mission in 2023. This will go towards funding two demonstrator sites in Birmingham and Liverpool which will foster research and trials associated mental health interventions, in partnership with industry.[37,38] A recent report by Lord O'Shaughnessy proposed methods of transforming the way that clinical trials are conducted in the UK.[39] In order to reduce the timeline of clinical trials, he suggests the implementation of Clinical Trial Acceleration Networks (CTANs); collaborative establishments between private, public, academic and charitable sector organisations that address common problems and design scalable solutions. They aim to enhance trial quality and efficiency through multidisciplinarity, fast and streamlined approval, and innovative trial design. The latter includes use of digital tools, access to data and ongoing communication between sites, co-ordinators and sponsors.	•

		The UK government have since set a goal of reaching a 60-day turnaround time for all regulatory approvals, created a new NIHR Research Delivery Network (RDN) for England from April 2024, and have developed the CTANs into Clinical Trial Delivery Accelerators (CTDAs)to support both commercial and non-commercial trials.[40] There are two CTDAs currently running, in the areas of dementia and vaccines. Since the aim is to focus on areas that have a high unmet need, and large addressable market, mental health appears to be a very suitable candidate for a future CTDA.	
Trials do not translate to the real world	**Heterogeneity of mental health conditions**	In discussing the heterogeneity of mental health conditions, the literature generally focused on the identification of, and acting on psychiatric subtypes.[41–44] There is some interest in the opportunities presented by machine learning, specifically supervised and unsupervised statistical approaches to identify putative subtypes in mental health patient populations.[44] They emphasise that subtype identification should be linked with a specific outcome or question. The study protocol, 'The Biological Classification of Mental Disorders' (BeCOME) is also raised for the in-depth phenotyping and omics characterisation of individuals with mental health conditions on the depression and anxiety spectrums. Launched at the Max Planck Institute of Psychiatry in Germany in 2015, BeCOME spans many levels from omics, cellular and imaging data to psychophysiological parameters as well as self-reported symptoms of mental disorders, personality traits and lifetime exposure to trauma and other environmental risk factors. Machine learning is applied at BeCOME, too, for the identification of biology informed diagnoses that could convey information on the individual therapeutic needs.[43] There is further support for addressing biological mechanisms with elements like epigenetic mechanisms, HPA axis responsiveness, synaptic and neuronal plasticity changes as well as neurotransmitter imbalances highlighted in particular.[41,42]	• Pharmacological interventions

		Interestingly, big data and machine learning have been envisioned in pain research for the development of a composite biomarker, and to identify patterns in self-reports of pain via text mining tools.[45]	
	Trial populations are not representative of the population who will take/use the intervention	**Trial population not representative** To address underrepresented populations in trials, some authors suggest open data repository to which real-life data is collated internationally. For some, this is the ideal mode of meaningfully capturing heterogeneities and long-term behavioural changes. The machine learning models would be subject to continuous assessment for validity to ensure that identified biomarkers are accurately representative of as diverse a group of patients as possible.[46] Pain research and research on rare diseases have also explored the option of collecting and exploiting longitudinal data.[47,48] Tracking change in reported pain symptoms over time is anticipated to provide valuable insight in pain development.[47] For rare diseases, the longitudinal effect has the potential to provide insight despite the often small trial participation.[48] **Marginalised groups are less represented in trials** Specific attention is also paid to strategies aiming for a maximum representation of marginalised groups.[49–51] Barriers to participation, which disproportionately affect underrepresented communities and strategies to overcome these[49,50,] include, but are not limited to: • Research tools and information forms that are translated, culturally adapted and locally validated (with sensitivity to alternative medicinal, recreational and ceremonial meanings) • Inclusion of representatives from indigenous communities in research design • Avoidance of stigmatising or embarrassing terminology	• Pharmacological interventions • Medical devices • Digital therapeutics

		• Gender matched research staff • Advisory boards specifically for cultural barriers • Care duty support • Financial reimbursement for time • Transport support • Facilitating accessibility and/or choice of sites • Culturally acceptable incentives • Support for people without medical insurance • Facilitation for religious or social commitments • Flexibility around employment needs • Focus on building trust and confidence It is important for such measures to be proactive. This means that, not only do the strategies need to be pre-emptively implemented but also continuously monitored and adapted where insufficiencies or new barriers are identified.[51] Similar trainings to elevate sensitivity to the needs and challenges in the trial population has been a regular part of HIV research.[52] This happens particularly in combination with cultural contexts to generate appropriate stigma reduction techniques.[53,54] As with mental health research, HIV research aims to increase diversity in clinical participation to ensure the representativeness of findings, and the proactive monitoring of the appropriateness of recruitment strategies is encouraged.[55] **Strict exclusion criteria**	

		RCTs studying schizophrenia may represent only about a fifth of the real population with schizophrenia spectrum disorders.[56] Moreover, the underrepresented population may be those at a higher risk of admission for psychosis than RCT eligible patients. With this in mind, there is need for an increased focus on these ineligible populations to address the treatment needs of those not represented in most RCTs. Additionally, the validity of exclusion criteria as a whole has been questioned, and it has been argued that reviewing exclusion criteria for RCTs requires background knowledge to intuit the rationale for the right criterion in addition to a labour-intensive review of existing evidence.[57] Further to this, the use of AI (e.g., natural language processing) has been encouraged in future research to support and expedite the review of existing evidence to ensure more accurate exclusion criteria.[57]	
Regulatory uncertainty			
Pricing and reimbursement models varied and complex		The difference in reimbursement models between private and public providers can be challenging to navigate, but there has been a move to harmonise this in the US, where a recently reintroduced bipartisan bill titled “Access to Prescription Digital Therapeutics Act of 2023” will expand Medicare and Medicaid to include digital therapeutics.[58] Somewhat similarly, an overarching body of governance has been recommended in the field of antimicrobial resistance (AMR). Due to the field suffering from a low return of investment (ROI), Roope at al. envision a global regulatory body that would oversee the antimicrobial drug development efforts. This would allow for coordinated global efforts on developing the pipeline of antimicrobials by nationally determining spending contributions.	• Medical devices • Digital therapeutics

		They suggested the WHO to serve as the governing regulatory body.[59] Regulatory frameworks such as the NICE Evidence Standards Framework (ESF) for digital health technologies require more intensive health economic analysis when the financial risk to the health system is highest. This framework aims to support local and national purchasing decisions around digital health technologies in England, and to help developers to plan the generation of their evidence base. This framework was co-designed with healthcare commissioners and innovators, and continues to closely monitor the landscape to ensure that it is up to date.[60]	
Regulation time consuming and resource intensive	Complex regulations that developers struggle to understand	The **variety of regulatory pathways** can make the process time consuming for developers. This is a particular challenge for digital interventions, as regulatory bodies are struggling to catch up with innovation in this area. Government and regulatory agencies are working on the definition of ad hoc regulatory pathways able to respond to the specific features of digital therapeutics and to their pace of technological change (e.g. DiGA). However, more centralised pathways should be adopted to drive future innovation and enhance patient access to digital therapeutics in general.[61] While RCTs are considered the gold standard in clinical trials, these can be challenging for digital therapeutics where a clear placebo cannot be established. Traditional trials can therefore be complemented with real world data. Post-marketing research to observe whether newly approved digital therapeutics maintain safety and efficacy in the real-world should be continued through manufacturers and academia.[62]	• Medical devices • Digital therapeutics

		Wider policy changes would also be able to ease regulatory barriers with additional, targeted market protections and expedited review to achieve adequate return on investment.[28]	
	Progression down wrong development pathway	*[No solutions identified]*	•
Lack of regulatory/IP incentive		*[No solutions identified]*	•
Inability to patent/protect digital therapeutics		*[No solutions identified]*	•
Developers opt for unregulated wellbeing market		There are a growing number of digital therapeutics that have not gone through a regulatory process and are instead marketing themselves as wellbeing applications. It is important for patients and clinicians to easily understand if a digital health product is regulated and if so, if they have been held to an appropriate evidentiary standard.[63] This should be available through a comprehensive, consolidated, and publicly available repository, which includes transparent information on public, private, or government ownership, public launch date, durability, and version history, so that the general public can make informed choices.[64] One solution to improve the rigour of app development, is to develop partnerships between academic researchers and health technology companies to test publicly available apps. This can allow for quality control standards to be applied to an unregulated market while capitalising on the strengths of the commercial sector.[64]	• Digital therapeutics

		Engagement with evidence-based digital interventions can be improved by integrating these into healthcare delivery services (i.e. being available via prescription).[65]	
Developer/Investor Concern that the Mental Health "Market" is not attractive			
Treatment Gap	Healthcare professional attitudes and perceptions	Improving mental health literacy in healthcare providers will help to improve their ability to recognise these disorders in patients and suggest appropriate treatment plans. Community campaigns could be implemented, aimed at increasing awareness and education. This can help to harmonise the understanding of what treatment options are available and what healthcare providers are able to offer. Providers in LMICs where there are poor mental health resources should target structural barriers by improving service availability and accessibility.[66] The problem of stigma within healthcare services should be approached from an organisational culture perspective and a quality of care perspective (developing metrics and targets into health and safety). Accreditation standards could also be put in place.[67] Healthcare professionals can struggle to prescribe and adhere to digital mental health interventions. Focus should be on promoting hybrid models of care that include multiple modes of intervention, including digital.[68] Clinicians may be more engaged with digital interventions, if there is a higher level of involvement at the development stage with academics and industry stakeholders.[69] This also allows for novel interventions to be integrated into existing care modes, and validated as the technology evolves. Evaluative frameworks such as Just-in-time adaptive intervention (JITAI) and Multiphase	• Pharmacological interventions • Medical devices • Digital therapeutics

		Optimisation Strategy (MOST) can also be applied to determine when these digital interventions are most appropriate.[70]	
	Low Treatment Seeking	**Perception of not needing treatment** One factor that contributes to the widening treatment gap is the large number of people who do not seek treatment for an existing mental health condition. However, to effectively reduce the population burden it has been suggested that the priority should be on improving the quality of care for existing people receiving treatment.[71] The development of effective and culturally appropriate interventions for mental health conditions that can be implemented in low-resource settings has been an important step towards providing appropriate support to people experiencing mental health symptoms. However, the limits of what these interventions can achieve in the absence of social and economic change must be acknowledged.[71] **Fear of treatment** Many people may be fearful of medical devices in particular. Innovation must therefore be justified in terms of meeting therapeutic need and resisting the technological imperative. In Europe, pre-market oversight of medical devices is decentralised and relatively light-touch (especially for non-invasive devices) in terms of evidence to support statutory safety and performance requirements. While this can promote innovation, the circumstances under which a product is able to rely on evidence of similar devices should be narrowed, to encourage new clinical trials being	• Pharmacological interventions • Medical devices • Digital therapeutics

		conducted. This will allow for increased confidence from end users in terms of its safety and efficacy.[72] Pharmaceuticals are another area associated with apprehension due to the potential adverse effects. Appropriate prevention and early management of these effects can enhance the net benefits of the medication. This can include appropriate dosage and monitoring of a medication with a health professional to determine how beneficial the medicine is and whether complementary interventions are required.[73] **Stigma of mental health conditions** Campaigns that aim to improve education and awareness around mental health should be developed and implemented to reduce stigma. This can be adapted for a variety of stakeholders, such as healthcare providers (as above), the policymakers, and the general communities.[66] Anti-stigma interventions can tailor messages both to people with a mental health conditions and to the wider public. It may be that helping people to understand and better support others with a mental health condition is a more effective approach than simply challenging assumptions about mental health.[74] Anti-stigma programmes should be adapted to the appropriate resource settings; especially for LMICs in order for them to be effective. This can be achieved through consideration of the cultural context, and aligning the messaging to the traditions or values of a country.[75] Stigma is also a prevalent barrier within HIV research, and education and awareness have similarly been cited as key facilitators for reducing this[52]. Additionally in cases where stigma is	

		higher in certain demographics, promoting diversity in clinical trials is even more important.[55]	
	Shortage of mental health professionals	While there is a clear need for an increased number of mental health professionals, especially in LMICs, it is also imperative that other healthcare providers are well trained to understand mental health.[76]	• Pharmacological interventions • Medical devices • Digital therapeutics
	Patient (6.14) and Health Provider (6.15) decision-making challenges	*[No solutions identified]*	•
Low user engagement (digital)	Digital divide	When adopting digital interventions on a national level, strong engagement can only be achieved if work is done to reduce the digital divide. Solutions for this include integrating apps into the existing local or regional digital health ecosystems, training programmes to improve digital skills, and making the intervention accessible regardless of language, culture, or disability.[77] Access to hardware or software is a significant barrier to engaging with digital interventions. This can be improved through the provision of free devices through a donation scheme, and increasing access to internet. Healthcare providers must also take the digital divide into account. They need to be aware of and actively facilitating potential digital interventions but also continuing to offer non-digital alternatives for those not yet able to engage.[78]	• Digital therapeutics
	Lack of reporting on and improving	It can be difficult to determine the extent to which a digital intervention has been engaged with and used appropriately, and this	• Digital therapeutics

	engagement strategies	can prove challenging when reporting on its efficacy. A framework for reporting trial adherence should be applied. A five element framework was proposed which covers the following broad areas: (1) an intervention statement that defines what it means for a participant to have used an intervention as intended, (2) rate of uptake (i.e. downloads of an app), (3) level of use (i.e. number of times the app was launched and how long was spent using it), (4) duration of use (i.e. weekly use patterns), (5) number of participants who completed the intervention as intended.[79]	
	Cultural adaptation challenges (digital)	A resource-saving possibility could be to use the high number of already existing and evaluated psychological treatments and to culturally adapt them for new target groups.[80] As referenced above, digital interventions are significantly more effective and engaging if they have been developed with cultural contexts in mind. This also includes tailoring pre-existing psychological treatments for new target groups.[80] This is a relatively low resource solution that does not require the development of a new intervention.	• Digital therapeutics
	Lack of co-production	In order for co-production in mental health research to be productive and valuable, it must be well considered and planned to ensure power is shared effectively.[81] The National Collaborating Centre for Mental Health suggested a number of solutions to commonly faced barriers in co-production. These include educating stakeholders on the value of co-production, recognise power differentials, and supporting various methods of contribution for people with different complexities of mental health need.[82] They also promote co-production at all steps in the commissioning cycle, and encourage joint ownership.	• Pharmacological interventions • Medical devices • Digital therapeutics

		In terms of digital interventions, the involvement of end users can help to reduce barriers slowing uptake in relation to both effectiveness and accessibility. For instance, a co-produced training programme for digital skills may be more effective in minimising the digital divide.[83]	
Poor patient adherence (pharma)		Personal beliefs about the negative consequences of using psychiatric drugs as well as environmental influences are the major factors leading to poor adherence. The latter may include cultural context, daily routine, living conditions, and social support. To combat this, it may be useful to discuss perceptions of the disease and pharmaceuticals with the patient and their family.[84] Having information on the perceived health benefits was a key facilitator, along with having a social support network and reminders for when to take the medication.[85]	• Pharmacological interventions
Affordability of mental health treatment		**Marginalisation** Marginalisation and social exclusion present multiple heterogenous barriers to access mental health services. Intensive cross-sectoral collaboration is thought to be necessary to develop policy and services at a more general level. One area of acute need is enhanced data collection, as deaths and health service use in excluded populations are largely invisible. In this line, Area-based measures of social deprivation across high income countries have allowed the assessment of the impact of less extreme social inequalities. These, in turn, have resulted in cross-sectoral policy initiatives in response. Literature calls for a similar line of action for the marginalised populations.[86]	• Pharmacological interventions • Medical devices • Digital therapeutics
Lack of investment into mental health interventions		While not a direct challenge but rather a result of an unattractive market. The literature does discuss methods of improving investment into developing mental health interventions.	• Pharmacological interventions • Medical devices

	Outcome-based financing mechanisms such as social impact bonds (SIBs) or research impact bonds differ from traditional investments in that payment is made on delivery of results. This allows developers increased financial and operational freedom as there are no activity-based agreements, and therefore facilitates increased innovation and the testing of new approaches. Impact bonds also promote collaborations between different types of organisations in the interest of reaching effective outcomes. SIBs have been implemented in healthcare systems for the delivery of interventions but there is the potential for this strategy to be used for the R&D of mental health interventions as well. Public and private partnerships are also key for fostering innovative and effective developments in this area. For instance, the US National Institutes of Health (NIH) set up the Accelerating Medicines Partnership in 2014 in collaboration with the FDA, and private and non-profit organizations to support the development of new diagnostics and treatments.[87] One of these partnerships focuses on interventions for schizophrenia and has established a global research network with 43 study sites around the world.[88] They have also made their research data publicly available to the scientific community to share resources and tools more widely.[89]	• Digital therapeutics

D.1. Adjacent Solutions

We have conducted targeted literature searches to identify potential solutions that have been adopted in areas outside of mental health to address similar challenges in their own fields. The transferability of these solutions has not been tested and thus remains tentative. The four areas have been chosen for particular challenges in mind:

- The area of **pain** research suffers from a lack of biomarkers;
- **HIV** as a condition is often associated with stigma;
- Tackling **antimicrobial resistance** is hindered by the low expected return on investment (beyond scientific challenges);
- Developing medical countermeasures for **rare diseases** is challenging due to the low number of patients available to participate in clinical trials.

D.1.1. Pain

A significant challenge when developing interventions for pain is the **lack of biomarkers**. As in mental health research, there is no clear scientific method to measure the severity of symptoms. This is particularly challenging when developing pharmaceutical interventions.

Biomarkers based on **neuroimaging** (e.g. MRI, EEG) are generally more common as they are more translatable to animal models, and thus allowing the development of novel analgesic targets, compared to self-report measures. There is also potential for more specificity, especially in terms of different locations and types of pain.[36]

Novel research has utilised **multimodal approaches** that take several sources of data into account. This may include a combination of brain imaging data, patients' self-reports and other related physiological data[90]. In terms of pain, these other factors may include metabolic abnormalities, oxidative stressors, and nutritional deficiencies.[91]

With large amounts of data, **AI and machine learning techniques** can then be applied to identify patterns in the data and develop a composite biomarker.[92,93] In the case of self-reports, this has included text mining and analysis to determine the level of pain being experienced.[94] Pain is also a highly complex and variable condition so there have been suggestions that composite biomarkers should be validated using personalised data sets and correlative designs.[45]

Other possible solutions that have been used to circumvent the lack of biomarkers are **longitudinal studies** which can track the change of pain symptoms over time[47], and **epigenetic markers**[95]. Results from existing interventions themselves can also produce useful data that can be applied to future research.[96]

Evaluation frameworks for novel biomarkers have been discussed and it was suggested that a similar model to the CDC's ACCE Model Process for Evaluating Genetic Tests[97] could be implemented. This would evaluate biomarkers based on four broad areas; (1) Analytic Validity (2) Clinical Validity

(3) Clinical Utility, and (4) Ethical, Legal, and Social Impacts.[98]

D.1.2. HIV

Research on HIV is often held back by the **stigma** around the condition. This can prevent the involvement of PWLE throughout the development pipeline, particularly in clinical trial recruitment. Meaningful inclusion of PWLE in the design, development, implementation and interpretation of interventions is required if interventions are to be effective.

The major approach to combatting this stigma has been improving **education and awareness** across a number of domains including the individual, organisation, and policy levels. Health providers should be provided with educational and training programs, and facilities should enact policies that prevent discrimination against PWLE. Such policies are most successful when developed in a participatory manner, and routinely monitored after implementation.[52]

Stigma around HIV can be particularly prevalent in LMICs due to the higher prevalence of HIV in LMICs, and solutions should therefore be tailored for these countries. **Cultural context** must be taken into consideration and stigma reduction techniques should account for variation in verbal ability and willingness to participate in group sessions, which may vary between different sub-groups.[53,54]

Many PWLE feel uncomfortable publicly attending clinical trials. One solution to this is setting up **clinical trials** to protect participants' confidentiality. The purposeful masking of services could pose problematic from a research ethics standpoint, so it would be imperative to adhere to the principles underlying research integrity and ethics.[99]

Improving diversity in clinical participation is key to ensuring that the results are reflective of the population. This can be challenging when stigma may be higher in certain demographics. To promote clinical trial involvement for participants of colour, facilitators may include culturally sensitive informational materials about the trials, outreach workers, and peer support groups to assist patients with adherence to study protocols. In the development of trials themselves, researchers may consider oversampling of a community, modifying eligibility requirements, and focusing on the clinical entities that are over-represented in PWLE of colour.[55]

D.1.3. Antimicrobial Resistance

A key challenge in the field of antimicrobial resistance (AMR) is that the expected return on investment (ROI) is low. When a new antimicrobial is developed and authorised, current scientific guidance suggests that the actual use should be delayed for as long as possible to limit the potential development of AMR. Once new antimicrobials are used, these will likely have limited patent period left or the patents already expired, which will allow low-cost generics to enter the market. As a result of unattractive ROI, many large pharmaceutical companies have withdrawn from the R&D of antimicrobials. The solutions to this

challenge, both proposed and already implemented, can be broadly categorised into three categories: global stewardship and a 'tragedy of the commons' approach, market incentives and an improved health technology assessment.

A **global stewardship approach** recommends establishing a global regulatory body that would oversee the antimicrobial drug development efforts. This would allow for coordinated global efforts on developing the pipeline of antimicrobials by nationally determining spending contributions (for example a target of 0.01% of GDP on health[100]) that are reviewed and ratcheted, a global scientific stocktake every five years.[101] This global regulatory body could be hosted by the World Health Organisation (WHO) and would coordinate any global push or pull incentives that were put in place. A global hub for development and policy to take place would include a variety of stakeholders, such as SMEs, charities, public funders and IP specialists.[102]

Market incentives, both push and pull incentives, were also a proposed solution to increasing the global antimicrobial drug pipeline. Market incentives ranged from the direct funding of trials (pre-approval) to more complex **delinkage models.**[103,104] Delinkage models are a way of separating economic success from the volume of sales of the drug sold. Volume-delinked models would provide compensation to companies regardless of the volumes of sales. This could either be through **partial delinkage**, where milestone payments are provided throughout the R&D process or **complete delinkage** that would provide a one-time payment (roughly $1B per product) that serves as a patent buy-out.[59,100,105] The UK and Sweden have trialled a 'volume-delinked subscription model',[106] the US has proposed a similar model in the PASTEUR Act.[107]

Health technology assessment agencies (HTAs) play an important role in creating confidence that if valuable technologies can be developed, they will later be reimbursed at a level that matches their value. To play their role more effectively and increase investor confidence, it is suggested that HTA agencies should broaden their methodological tool kit to incorporate long-term policy goals, such as containing resistance, as part of their evaluation criteria and build a more attractive antimicrobial R&D market.[108]

D.1.4. Rare Diseases

A key challenge in the field of rare diseases is that low numbers of patients can participate in trials and therefore, generating sufficient data for regulatory approval in RCTs becomes a bottleneck. Proposed solutions to these challenges include adaptive design methods (including innovative statistical methods), the establishment of network trials and the use of real-world data and the patient voice.

To reduce the average size of participant cohorts in a trial, there are a number of adaptive design methods to choose from. **Sequential trials** can be used, where data are analysed intermittently throughout the trial to guide decisions on ending early due to

safety concerns, efficacy, futility, or some combination of these.[48,109] **Factorial studies** can also reduce the sample size, where two (or more) treatment options are carried out simultaneously, which provides answers to multiple research questions within the same study population.[110] **Longitudinal studies** also offer an opportunity to study the long-term effects of a treatment option while maintaining a relatively small sample size[22]. Alternatively, innovative statistical methods can be used to overcome the challenges of small sample sizes. For example, **adaptive RCTs** can be used to narrow for a selection of doses rather than rejecting the null hypothesis; the conventional frequentist threshold can be increased; and the results can be incorporated into larger studies such as a **meta-analysis** or a **Bayesian framework.**[111,112]

Network trials and **collaborative studies** were also cited as a method of increasing the sample size and increasing the heterogeneity of samples in rare disease trials.[113] Fostering collaborations between research institutions, hospitals, and clinics to pool resources from multiple centres increases the sample size and enhance the statistical power of the study.[114]

To alleviate the challenges of requiring a large randomised clinical trial (RCT), incorporating '**real-world data'** is suggested in conjunction with an RCT. This would include the data from health outcomes that are not quantifiable based on data collected in RCTs but would centre the patient's voice in the process.[115] Cited examples of real-world data includes the 'near normalisation of all aspects of patient lives.[116]

D.2. Conclusion

The systematic literature review and targeted desk research identified and summarised solutions around challenges and barriers. It is of note that some of the solutions identified do not map neatly onto a single barrier in our framework. This may not be unexpected as there are interdependencies across the barriers themselves.

The lack of biomarkers is a significant challenge that has increased associated risks and development costs. There has been a general shift away from behavioural models towards biological markers across the industry. A potential solution was suggested that would involve a registry of continually updated real world data that can be used to complement or replace RCTs. To improve trial participation, the needs of vulnerable and marginalised individuals must be taken into account, by improving the accessibility of trial information as well as making the trial itself more flexible.

In terms of regulatory complexity, there is a clear call for more centralised pathways, especially for digital interventions. Where innovation is moving at such a fast pace, regulatory bodies must monitor the landscape and tailor the standards of evidence required, where necessary (e.g. where RCTs are not appropriate).

Developing interventions for the mental health market has been considered unattractive, due to the treatment gap

and lack of engagement from patients who are seek treatment. A notable solution that was mentioned in the literature was improving knowledge and understanding around mental health conditions themselves and potential interventions, and how these can be implemented. This can help to reduce stigma and manage patients' expectations. Another key consideration was cultural contexts, which should be taken into account when integrating an intervention into a healthcare system, to promote engagement with interventions, especially in LMICs.

Moving from traditional methods of investment into novel approaches such as outcome-based financing may also increase innovation, and in turn shift the perception of the mental health market. Innovation and appropriateness of R&D can be further enforced by encouraging partnerships between private and public establishments.

D.3. References

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Appendix E Number of clinical trials utilised in the calculation of average trial costs

	Phase I	Phase II	Phase III
All health conditions	**29,460**	**27,151**	**12,270**
Mental health	**1,066**	**449**	**268**
Anxiety			
Generalized anxiety	10	37	28
Obsessive-compulsive disorder	15	24	14
Social anxiety	6	8	10
Panic disorder	4	3	4
Body dysmorphic disorder		2	
Post-traumatic stress disorder	43	78	18
Depression			
Postpartum depression	7	6	4
Major depressive disorder	459	257	147
Psychosis			
Schizophrenia	353	102	87
Bipolar disorder	118	52	36
Premenstrual dysphoric disorder		1	

Source: Citeline. Note: All health conditions include oncology, infectious disease, Autoimmune/Inflammation, Metabolic/Endocrinology, Cardiovascular, Genitourinary

Appendix F Prioritisation workshop stakeholder breakdown

F.1. Overview of interviews conducted by stakeholder group

Stakeholder group	Subgroup	Count
Developers	Digital therapeutics	14
	Pharmaceuticals	4
	Psychedelics	3
	Medical devices	3
Funders/investors	Government bodies/research foundations	10
	Angel investors/Venture capital	2
	Others	1
Healthcare providers	Government bodies	4
	Professional bodies	2
	Private clinic	1
	Psychedelics	1
Policymakers/ Regulators	Government bodies	2
	National/State Competent Authority	4
	Supra National	1
External actors	Advocacy group	3
Total		**57**

F.2. Number of participants by stakeholder group and breakout session*

Stakeholder Group	Breakout Room 1	Breakout Room 1	Breakout Room 1	Total
Developers	3	3	3	**9**
Experts	1	1	1	**3**
Investors/Funders	1	0	1	**2**
Policymakers/ Regulators	1	1	0	**2**
PWLE	3	3	3	**9**
Total	**12**	**12**	**11**	**35**

* In addition, representatives from Wellcome were in attendance.

Appendix G Case Study (digital devices): gameChange

G.1. Summary

gameChange	
Type of intervention	Digital
Barrier(s) encountered	Flexible recruitment needs for clinical trials, Developers engagement with regulatory affairs

The gameChange VR project addresses agoraphobia-related avoidance and discomfort in individuals with psychosis. It leverages virtual reality (VR) therapy to simulate everyday scenarios, guided by a virtual coach. This innovative approach fills a critical gap in the treatment of psychosis, as conventional therapies often lack accessibility and focus on social interactions. In this line, it is important to note that agoraphobia is very rarely treated directly in people with psychosis, as most individuals with psychosis primarily receive medication, with only around 5% estimated to undergo talking therapy.[1]

The project, funded by the UK's National Institute for Health Research (NIHR), involved a diverse team of experts and individuals with lived experience of psychosis. The VR therapy underwent a clinical trial involving 346 patients across nine NHS trusts, demonstrating significant reductions in agoraphobic avoidance and distress compared to usual care. Challenges included technical issues and regulatory complexities, which were successfully addressed. The involvement of individuals with lived experience played a pivotal role in shaping the project, influencing scenario selection, outcome measures selection and development, and accessibility considerations.

G.2. Introduction

Psychotic disorders, encompassing conditions like schizophrenia, psychosis in bipolar disorder, depression with psychotic features, and substance-induced psychoses, represent a significant and growing public health concern. Recent research indicates that the occurrence of psychotic disorders may be more prevalent than initially thought, with an estimated incidence of 26.6 cases per 100,000 person-years.[2] Many individuals with psychosis experience social withdrawal and isolation, which has far-reaching implications for both mental and physical well-being. A sedentary lifestyle is common among these patients, and their life expectancy is on average nearly 14.5 years shorter. The reasons for this are complex but they include the presence of preventable conditions such as hypertension, diabetes, and cardiovascular disease.[3] However, they are also likely to include social factors such as isolation, and socio-economic factors.[4] Research indicates that a substantial proportion of patients with psychosis report levels of anxious avoidance comparable to those seen in agoraphobia.

Agoraphobia is defined as intense fear and avoidance of being alone or in public spaces where escape might be challenging or help not available in case of sudden incapacitation.[5] These avoidance behaviours may stem from a variety of factors, such as paranoia, auditory hallucinations, social anxiety, negative self-image, panic attacks, and a lack of confidence in one's ability to navigate challenging situations.[3]

Consequently, these individuals harbour amplified thoughts, leading to the avoidance of social interactions or the adoption of in-situation defence mechanisms.[3] People with psychosis suffer from social isolation and have lower-than-average incomes.

The gameChange project was developed to support people with psychosis, more specifically those with agoraphobia-related avoidance and discomfort during everyday activities.[6] Conventional approaches to address agoraphobia have faced limitations in accessibility and effectiveness, creating a pressing need for new interventions. Currently, agoraphobia is present in approximately 1.7% of the general population,[7] while only about 5% of people with psychosis receive psychological therapy.[2] For those who do receive therapy, it rarely focuses on the difficulties with social interactions, despite many experiencing intense fears about being outside and in public.[2] This treatment gap is exacerbated by a shortage of clinicians trained to deliver specialised therapy.[2]

The gameChange project was funded by the UK's National Institute for Health Research (NIHR) for a total amount of £4m and leverages the immersive capabilities of VR to provide a unique therapeutic experience. It involves immersive computer-generated simulations of common scenarios, such as being in a café, bus, or doctor's waiting room, while guided by a virtual coach. Hence, patients are encouraged to experiment with dropping defence behaviours and address their fears. The therapy consists of six sessions, and a staff member is present to assist with equipment and help plan homework tasks for reinforcement.[3]

G.3. Development Story

The gameChange development was originally conceived as a three-year project (but extended due to the pandemic) led by a collaborative effort involving a diverse group of experts, such as clinical psychologists, designers, software developers, and individuals with first-hand experience of psychosis. Spearheaded by a team of mental health professionals, researchers, and virtual reality (VR) technology experts, the project was delivered by researchers at the University of Oxford and Oxford Health NHS Foundation Trust. Partners included Oxford VR, a University of Oxford spinout overseeing software development, the McPin Foundation, a UK charity which advocates for the involvement of people with lived experience (PWLE) in mental health research, the Royal College of Art, NIHR MindTech, and nine NHS Trusts across England.[3,8]

The first step involved examining the prevalence rate and evaluating the extent to which people desired a change in the situation,[8] as part of a comprehensive needs assessment. This included surveying 1,800 patients to identify the specific challenge of agoraphobic avoidance and determine its prevalence within the target demographic.[38]

The development of the automated VR therapy took place over the first 12 months of the gameChange study. The design process was person-centred, which meant this method placed a strong emphasis on incorporating the

perspectives and needs of end-users at every stage.[3] The clinical psychology team in Oxford held overall responsibility for design decisions.[38] The process included setting the initial design brief, conducting workshops, individual sessions, workflow production, scripting for the virtual therapist, prototyping scenarios for feedback, 3D modelling of environments, creating virtual characters, software implementation, extensive user testing, and quality assurance.[3]

The next step involved developing a treatment brief which built on previous studies showing the efficacy of VR in treating anxiety in patients with psychosis. The treatment structure and delivery automation were influenced by prior VR interventions for fear of heights and persecutory delusions.[3] Furthermore, the treatment brief confirmed that it is not only exposure to a distressing situation that is crucial for clinical change, but actively testing out fears with the dropping of defence behaviours.[3] It outlined a treatment structure for addressing anxious avoidance in psychosis, involving 30-minute sessions with varying levels of difficulty and automation using a virtual coach in a virtual office setting.[38]

The input of users, particularly those with lived experience of psychosis, was central to design decisions. Over 500 hours of input were provided by 53 individuals. A Lived Experience Advisory Panel (LEAP) was established, consisting of ten individuals recruited from different centres participating in the clinical trial.[9,10] However, it is important to note that these were not people who took part in the clinical trial as participants. They played a key role in defining the scenarios and providing ongoing feedback throughout design and development.[3,10] Twelve design workshops were conducted in various locations together with McPin and the Royal College of Art, with participants providing input on scenarios, tasks, characters, and situational triggers. The added value of the McPin Foundation was that it provided a flexible and inclusive way of involving people from more diverse ethnicities, genders, and ages, allowing participants from across the country to contribute their experiences. It also allowed an independent and objective view of the design phase as these individuals were not familiar with gameChange, in contrast with the LEAP group.[3,11] Individual user testing sessions and workshops with NHS staff further informed the development process.[3] This stage of the process was led by staff at the University of Oxford.

In the subsequent script development of a virtual therapist, dialogues from both the virtual coach and other virtual characters were incorporated, as a vital component for automation. It was essential for the script to effectively communicate psychological principles, such as cognitive activation, in an engaging and accessible manner, while also ensuring that the therapy content remained relevant and appropriate for a range of different psychosis presentations.[3,11] Likewise, the psychology team identified and highlighted key fears and associated defence behaviours throughout the script. Preferences for the wording of

feedback and encouragement from the virtual coach were gathered from users in the design workshops. This iterative process resulted in an early draft of the script consisting of 100 pages. Role plays with and feedback from psychologists, developers, and PWLE were conducted and incorporated into the script. This process was repeated three times before the team reached the final script, which the LEAP reviewed and provided additional feedback on.[3]

In the next step, the project team produced scenario workflows, where they mapped out user journeys. The LEAP team initially generated a list of situations relevant to patients, which included being on the street, using public transportation, and waiting in places like banks or doctor's offices, among others. Here, a key decision was to decide which scenarios and activities (people would undertake in those scenarios) to keep or exclude due to its feasibility to replicate in VR or relevance to anxious avoidance.[3] Each LEAP member was asked to choose the three scenarios they considered most important. This approach aimed to ensure that each trigger was integrated into one of the final scenarios. The final six gameChange scenarios that were selected are: travelling by bus, being on a street, visiting a café, going to a pub, waiting in a doctor's office, and shopping in a store.[3] The development process resulted in the creation of an automated delivery VR treatment. During this stage, there were several technical challenges such as maintaining a stable and high-quality virtual reality experience for users wearing headsets, addressing issues like drifting, which can cause discomfort or disorientation,[11] and developing a procedure to decontaminate VR equipment during the COVID pandemic.[11]

In the final step, gameChange was subject to clinical testing and evaluation. It underwent a clinal trial across nine NHS trusts in England, the largest test of any VR therapy for a mental health condition.[12] Patients were randomly assigned to receive either gameChange VR therapy in addition to usual care or usual care alone. Results showed that the gameChange VR therapy group experienced significant reductions in agoraphobic avoidance and distress at six weeks compared to the usual care group.[12] Patients with more severe agoraphobic avoidance reported the most significant gains in the clinical trial.[10]

Concerning the clinical assessment, several challenges arose. The emergence of the COVID-19 pandemic presented a significant obstacle, especially for a therapy aimed at encouraging individuals to engage with the outside world when health authorities advised otherwise.[9,10] The recruitment was thus paused, which led to a six-month project delay.[9]

The pandemic has also put in question the clinical trial's original outcome measure. Initially, participants were going to be asked to assess their ability to tackle progressively harder tasks, from "Standing outside your home on your own for 5 minutes" to "Traveling on your own on the bus for several stops".[9] The primary outcome

measure was however changed to avoidance of, and distress in, everyday situations, evaluated using the newly developed self-report Oxford Agoraphobic Avoidance Scale (O-AS) .[9,11] This scale was developed as a response to the challenges that the pandemic posed to the study.

The culmination of this journey led to the certification of the automated gameChange VR therapy as a Class I medical device, in alignment with Directive 93/42/EEC.[3] This required hiring an external expert on the regulatory framework for medical devices because it was not clear to the researchers under which category gameChange would fit.[11] gameChange has undergone an Early Value Assessment (EVA) by the National Institute for Health and Care Excellence (NICE). gameChange has been recommended for use in the NHS for people with severe agoraphobia so that more research evidence can be collected.[13]

G.4. Lived experience perspective

Including people with lived experience (i.e. people who had faced challenges related to psychosis) in the design and development process of gameChange led to several benefits.[9] Developers gained first-hand insight into patients' day-to-day struggles. Through workshops, information was collected about specific situations that posed challenges to patients, ensuring VR scenarios resonated with their real-life experiences.[3] It also enabled the exploration of factors that made certain situations easier or more challenging, such as navigating queues, surveillance cameras, the number of people present, the level of attention received, and the surrounding environment.[10] This collaboration allowed fine-tuning of the VR experience, ensuring it offered an appropriate level of challenge for users across different difficulty levels.[39]

Feedback from PWLE also informed the appearance and characteristics of the avatar, named Nick. Some raised concerns about the avatar's lack of diversity, advocating for a more inclusive representation. Due to technological limitations, however, the program could only generate one avatar, restricting the ability to offer a range of choices.[10]

Throughout the testing phase, PWLE identified various bugs and inconsistencies within the VR scenarios and the observations were valuable in refining the program, ensuring that each level provided an appropriate balance of challenge without it being too easy or excessively difficult.[9,10] Hence, their input was invaluable in calibrating the VR experience to be engaging and beneficial for participants. Furthermore, PWLE influenced the choice of instruments used to measure health-related quality of life in the actual trial, where the standard EQ5D measure was replaced with a mental health-specific quality of life measure called ReQoL.[10]

In terms of inclusivity and accessibility, the project team recognised that some participants faced challenges leaving their homes to participate in the clinical trial. A key decision was made at the beginning of the study to allow therapy sessions in their residences to

accommodate these circumstances. Efforts were also made to ensure that any transportation expenses were covered, removing a potential barrier to participation, especially considering that some of the trial sites covered a large geographical area.[9,10]

Overall, according to interviewees, the collaboration with PWLE greatly enriched the study, influencing multiple aspects from scenario selection to outcome measures and accessibility considerations. As the lead of the lived experience advisor said: *"We had some impact around the actual instruments used to measure health-related quality of life that were used in the study, which makes me quite proud because we don't usually change or develop measures as a result of wishes of people with lived experience".*[10]

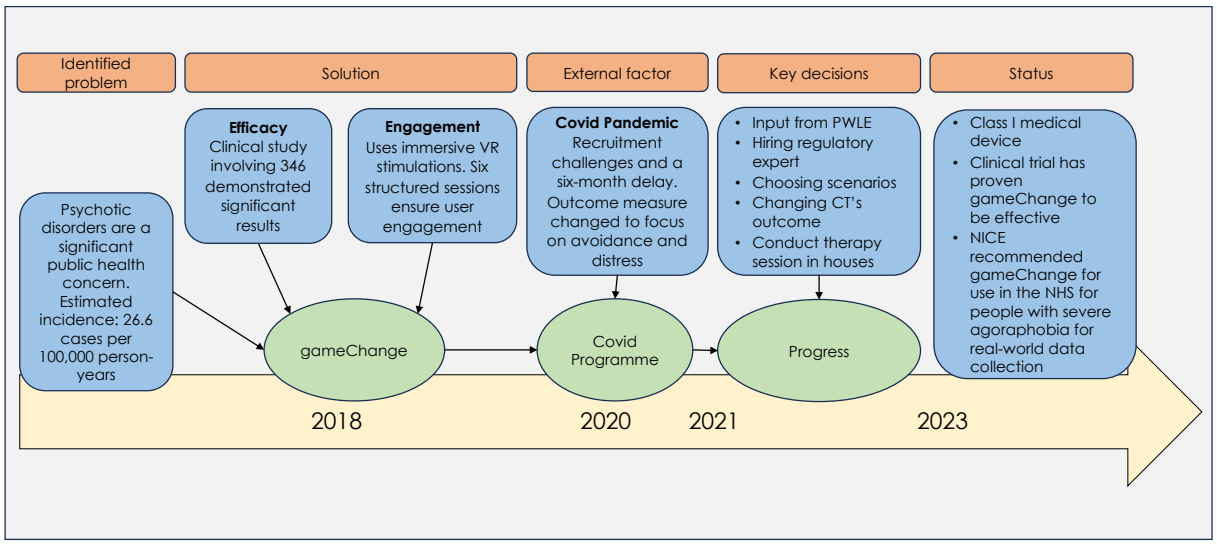
G.5. Conclusions

The gameChange project faced technical challenges in developing the therapy, related to maintaining a stable visual experience for users wearing headsets and addressing issues like drifting. Nonetheless, solutions were found, such as having a staff member present and by developing a procedure to decontaminate VR equipment during the COVID pandemic.[11] Additionally, the COVID-19 pandemic impacted recruitment and caused a six-month costed extension of the project. The pandemic also resulted in a change in outcome measures used in the clinical trial. Finally, regulations related to software as a medical device represented a new policy area for developers to engage with.

Key decisions in the development of the gameChange therapy included selecting relevant scenarios for VR and changing the outcome measure due to the pandemic circumstances. To make the development process inclusive and accessible, therapy sessions were also held in participants' homes, and transportation expenses were covered for everyone. These choices aimed to ensure a diverse and representative participant group while maximising the study's effectiveness.

The next phase of this project is to gather more research evidence for gameChange following the NICE EVA decision to provisionally approve gameChange for use in the NHS. Although the potential for scalability is promising, it may encounter some limitations due to language (the intervention is designed in English) and the need for certain spaces to safely use the VR, as well as expectations regarding hyper-realistic virtual reality by some users.[10]

G.6. Visual: Developer decision-making pathways with a timeline



G.7. Sources

Interviews:

Role	Organisation name	Date of interview
Professor of Clinical Psychology	Oxford University	28/09/2023
Senior Researcher/Lived Experience Expert	Oxford University	10/10/2023 and 02/11/2023

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Appendix H Case Study (digital devices): deprexis®

H.1. Summary

deprexis® – The clinically proven digital therapy for treatment of depression	
Type of intervention	Digital (Web-based)
Barrier(s) encountered	Lack of RCT design flexibility Navigating through the healthcare system can be time-consuming and resource-intensive Lack of training and guidance for healthcare professionals

deprexis® is a web-based digital therapeutic platform developed by GAIA, offering evidence-based self-help programmes for managing unipolar depression or depressive disorders. It includes ten modules with various resources, such as worksheets and exercises, adapting its approach to user preferences. Available in multiple markets, including the UK, the US and Germany, deprexis® can be accessed through subscription or prescribed by healthcare professionals as part of depression treatment. The platform was tested in several randomised clinical controlled trials (RCTs), which showed that it was effective in treating symptoms ranging from mild to severe. deprexis® has been approved in the UK (partially), the US and Germany.

The developers of deprexis® are faced with several challenges. The characteristics of digital therapeutics do not align well with standard RCT design. For example, the challenges of blinding and standardising digital interventions make it difficult to establish a suitable control group. Acknowledging this, regulators are actively producing guidelines and accelerated approval processes to address these specific challenges in digital therapeutics. Following approval, the company will need to navigate complex national healthcare systems such as NHS England to commercialise deprexis®. This is especially challenging for start-up companies with limited resources and experience.

During our consultation with various stakeholders, who proposed various recommendations for enhancement of the intervention, including incorporating more diverse representations within the built-in persona and scenarios in digital therapeutics, with the consideration of this at an early stage to promote inclusivity.

H.2. Introduction

The COVID-19 pandemic has significantly increased the demand for mental health services, causing concerns about workforce shortages. A 2022 survey of US psychologists found that 60% of psychologists report no openings for new patients, 40% have waiting lists, and nearly half experience burnout. Researchers and clinicians are exploring strategies to address the workforce shortage, including the exploration of ways to reduce the financial burden of obtaining a doctoral degree and encouraging diversity in mental health professions.[1]

In the UK, a shortage of consultant psychiatrists (one consultant psychiatrist per 12,567 people) leads to nearly a quarter (23%) of mental health patients having to wait over 12 weeks for mental health treatment.[2] The existence of hidden waiting lists

[xxvii] has detrimental effects on patients' mental health, and forces over three-quarters (78%) of patients on the hidden waiting lists to resort to emergency services.[2] In Germany, the number of psychotherapists per resident is higher. However, individuals still encounter waiting periods exceeding three months for an initial interview with a psychotherapist due to delays in the approval process of health insurance providers. This has prompted calls for advocacy for a three-week maximum waiting period.[3]

With over 40,000 people currently living with anxiety and depression in the UK,[4] the development of digital therapeutic interventions represents a potential solution to reduce the burden on healthcare professionals and address the prolonged wait times experienced by mental health patients. These interventions are characterised by accessible, self-paced options, remote monitoring capabilities, and the automation of routine tasks. In addition, digital therapeutics are easier to scale than in-person therapies, enable earlier intervention, and offer opportunities to further educate users on how to improve their mental health.[5]

deprexis® is a web-based digital therapeutic platform developed by the German company GAIA. It provides evidence-based psychological and psychotherapeutic therapies and exercises to assist patients in managing unipolar depression or depressive disorders. Primarily, it is a self-help programme based on cognitive-behavioural therapy (CBT) principles and dream state therapy, offering initial assessments, progress tracking, and tailored exercises. The service offers users 24/7 support, including virtual coaching in some versions.[6–8]

deprexis® offers ten modules on topics related to depression which users work through. These include worksheets, exercises, audio sequences, short texts (e.g. via text messages), and illustrations that help guide the users through the programme. As users make their way through the modules, the platform adapts tasks according to the needs, preferences and answers of the user. Progress is tracked using PHQ-9 (The 9-question Patient Health Questionnaire - a diagnostic tool introduced in 2001 to screen adult patients in a primary care setting for the presence and severity of depression[9]), and the user's mood is monitored through MoodCheck (an assessment tool used for bipolarity[10]). Both the questionnaires and the progression chats can be downloaded and shared with a healthcare professional.[11]

Available in multiple markets, including the UK, US, and Germany, deprexis® serves as both a direct-to-consumer product and a prescribed therapeutic intervention facilitated through healthcare providers or insurers (in the US and Germany).[7,12,13]

This case study will explore aspects of deprexis®' development, with a more in-depth review of the regulatory

[xxvii] A hidden waitlist in the context of healthcare refers to a waiting list where individuals have requested or are waiting for a GP referral to services, appointments, or treatments. The waitlist is unknown to the health service.[40]

approval pathway and commercialisation of the platform, including the barriers and challenges faced.

H.3. Development Story

GAIA, a digital therapeutics developer specialising in the development of mental and physical health products, started developing deprexis® in 2007. GAIA is one of the few digital therapeutics developers that have been able to extensively test their products in randomised controlled trials (RCTs). Since 2009, the company has conducted a total of 12 RCTs on the effectiveness of deprexis® and shared the results in peer-reviewed publications.[14]

The EVIDENT (Effectiveness of Internet-based Depression Treatment) trial, the largest RCT on deprexis®, received funding from the German Ministry of Health (BMG) in 2012. This study involved academic research groups from Universität Bern, Charité Berlin, Universität Bielefeld, Universität Hamburg, Universität Tübingen, and Universität Trier, alongside the developer, GAIA. The trial randomly assigned 1000 individuals suffering from mild to moderate depression to receive either deprexis® in addition to their existing treatment over a one-year period, or to remain on their existing treatment only (control).[15,16] The results showed that deprexis® is effective in reducing depressive symptoms and improving general well-being as well as participants' ability to interact effectively with others.[17] A health economic evaluation of the EVIDENT trial concluded that while adding deprexis® to participants' existing care regimen did not have a significant effect on total healthcare costs, it significantly reduced outpatient treatment costs.[18]

The finding that deprexis® yields clinical benefits was supported by a meta-analysis of 12 RCTs (including the EVIDENT trial). The analysis confirmed that the intervention is relevant for patients with a broad range of symptom severity, and in combination with a range of other treatments, including inpatient and outpatient psychotherapy as well as antidepressant medication. One RCT indicated that for patients suffering from severe depression, the combination of deprexis® and antidepressants may yield particularly large effects.[14]

It should be noted that the trials are mainly based on the German population, with the exception of one study based in the US,[17] which is not a representation of the global population. Despite the potential for further development and RCTs with diverse demographics, no such plans are currently in place. There is no indication of future research and development for deprexis®, and the specific reasons for this decision remain unknown, as the developers at GAIA have not expressed interest in engaging with further studies.

H.4. Regulatory Approval and Commercialisation

The three main markets for deprexis® are Germany, the US, and the UK. Therefore, deprexis® is required to obtain marketing authorisation in these three countries. The regulatory approval process for digital

therapeutics is relatively new, and in some countries, the requirements and classifications are still unclear, which can be challenging for developers to navigate.

H.4.1. Regulatory approval process

Germany

In 2019, Germany's parliament passed the Digital Health Care Act (Digitale-Versorgung-Gesetz, or DVG) to support and accelerate the digital transformation of the German healthcare system. The act includes the formalisation of "prescribable applications" (Digitale Gesundheitsanwendungen or DiGA). Digital health applications that receive approval are listed in the DiGA directory, enabling their prescription and reimbursement by German health insurance providers. In addition, the DVG created a Fast-Track Process for approval, overseen by the Federal Institute for Drugs and Medical Devices (BfArM). As part of this process, the BfArM is required to evaluate applications within three months from submission. Germany is now recognised as a leader in the digital transformation of its healthcare system.[19,20]

In February 2021, deprexis® was approved and recorded in the DiGA directory as a browser-based web application.[21] This was likely facilitated by the fact that the platform's developer, GAIA, and most of the RCTs that tested the intervention were based in Germany (including the EVIDENT RCT, funded by the German Ministry of Health). It has been noted that all data processing in connection with the use of deprexis® must remain in Germany as one of the conditions for approval.[21]

United States

In 2020, the US Food and Drug Administration (FDA) launched its 'Digital Health Center of Excellence' to support digital health innovation, e.g. by streamlining the regulatory pathway, while upholding FDA safety standards.[5] Earlier that year, triggered by the COVID-19 pandemic, the FDA had introduced an 'Enforcement Policy' for digital health devices addressing psychiatric disorders. Its goal was to increase the availability of virtual health services during the COVID-19 pandemic.[22] The policy granted the FDA discretion in relaxing specific regulatory requirements for digital health therapeutic devices, including online behavioural therapies.

[2827]Benefitting from this policy, deprexis® gained FDA temporary approval via the Emergency Use Authorisation (EUA[23]) pathway in July 2020.[5,24] With the act declaring the COVID-19 public health emergency expiring in May 2023, the FDA provided guidance on how to transition medical devices that received approval via EUA during the pandemic to operations under normal conditions.[25]

United Kingdom

The UK introduced the Early Valuation Assessment (EVA) in June 2022. Similar to Germany's DiGA fast-track process, the EVA rapidly assesses evidence of clinical effectiveness and value for money of new medical technologies in priority areas for health and social care, starting with digital technologies.[26] Unlike full NICE guidance, technologies selected for

EVA are not expected to have a complete evidence base before they can be recommended for use through EVA.[18] If recommended, NICE works with the developer to plan the collection of real-world data in the NHS, ensuring that it addresses remaining evidence gaps before a full NICE evaluation.[27] In this way, the EVA aims to speed up the commercialisation of digital interventions.

One of the priority areas NICE identified for EVA is mental health. In June 2022, NICE selected six digital therapeutic technologies for depression, including deprexis®, with a view to publishing findings in October.[26,27] This first EVA was completed in January 2023. The assessment concluded that deprexis® is cost-effective in treating people with mild to moderate depression. Of the six technologies evaluated, it was the only option recommended for people with severe depression.[28]

For each of the digital therapeutics, the EVA evaluated available evidence from RCTs, use of the intervention in the NHS' Improving Access to Psychological Therapies (IAPT) setting (NHS service offering short-term psychological therapies to people suffering from anxiety, depression and stress), and on economic benefit. However, the report also highlighted that the technology may not be the most cost-effective treatment option when compared with other standard treatment options. Furthermore, no evidence was available in the IAPT setting in the UK. There was only one study in Germany that included usual care or waitlist control as a comparator.[11]

Following the positive outcome of the NICE EVA, the next step for deprexis® is to collect real-world evidence before undergoing a full NICE assessment and converting the conditional recommendation into final NICE guidance. In order to achieve this, NICE, deprexis® UK distributor (Ethypharm Digital Therapy), and the NHS worked together to develop a plan on how to collect the evidence required for the full assessment. The developers are currently gathering additional data on deprexis®, collaborating closely with a primary care provider, The Grange Medical Centre (GP surgery) in Warwickshire. The implementation of deprexis® has been in pilot since 2022 and has recently expanded to clinics in Leicester and Liverpool.

H.4.2. Commercialisation and Access

For the commercialisation of deprexis®, GAIA entered into partnerships with companies in target markets: in Germany with Servier in 2015,[29] in the US with Orexo in 2022,[30] and with Ethypharm Digital Therapy in 2021 in the UK,[31] after a first trial by the NHS in 2018 as a part of NHS England's Improving Access to Psychologic Therapies programme.[31,32]

The pathway in which patients can access deprexis® varies slightly between the three countries.

In Germany, deprexis® can be prescribed by doctors or psychotherapists, with costs covered by the patient's health insurance. Patients who have already been

diagnosed with depression can provide their health insurance company with proof of the diagnosis to receive deprexis® without a medical prescription. Alternatively, patients can pay for the service directly via the deprexis® website. As previously mentioned, deprexis® has been fully approved and permanently included in the DiGA directory as a recommended digital therapeutics option.[21]

In the US, a prescription is not necessary for patients to access deprexis® to be fully or partially covered by their health insurance. The patients can also pay for the service directly.[33]

Similarly, patients in the UK can be prescribed deprexis® by doctors as part of their mental health treatment. However, it is currently only available via specific clinics that are part of the real-world data collection study addressing the evidence gap highlighted in the EVA report. Results from the study are expected in early 2024, with a subsequent full NICE assessment to determine if deprexis® will be recommended as a therapeutic in the final NICE guidance. Patients have the option to pay for the service directly.[7]

H.4.3. Barriers and Challenges

In navigating the regulatory system and commercialisation of deprexis®, three key barriers have emerged, shedding light on challenges within the digital therapeutic space. These barriers are outlined below:

Lack of RCT design flexibility

A major barrier to regulatory approval for digital therapeutics lies in the demand for evidence on effectiveness through RCTs, typically requiring a randomised double-blind placebo control. Defining suitable digital control conditions is a significant challenge, particularly in mental health research, where creating a homogenous control group is difficult due to diverse disease characteristics and various treatments. The stringency of digital control conditions in these trials may vary based on factors such as risk profile and the novelty of the intervention. Given the generally low-risk profile and the potential of digital therapeutics to enhance access to personalised care, some developers may opt for less stringent controls such as waitlist controls. Consequently, a slightly more robust mental health intervention RCTs often define the control group as 'treatment as usual' (TAU), with individuals continuing their existing treatments. The lack of a standardised TAU definition and its absence in medical specialty pose challenges, as opposed to well-defined placebos. This leads to the challenge of attributing changes in outcome solely to the experimental intervention, as variations in the control group's care could influence the result. [34,35]

While waitlist controls may lead to an overestimation of treatment effects, they could be considered in large-scale real-world studies. The iterative nature of software development meant that RCTs may not always be the most appropriate approach for evidence generation. A continuous assessment of effectiveness in real-world settings

would be the more appropriate approach to the regularly updated and changing digital technologies, emphasising the need for regulators and digital therapeutic developers' collaboration to establish best practices for robust evidence collection.[34–36]

deprexis® is one of the digital therapeutic interventions that secured regulatory approval by conducting various RCTs using TAU as the control group.[15] The support and funding from the German Ministry of Health likely played a significant role in this achievement, with specific conditions agreed upon to define the control group. This ensured level of robustness in evidence regarding effectiveness acceptable to the German regulator.[37] Consequently, this may have been an enabler in overcoming the barriers most developers faced to get their digital therapeutic interventions approved. The large amount of RCT evidence demonstrating the effectiveness of deprexis® may have also contributed to the approval of its use in the US.

In the UK, the introduction of the Early Valuation Assessment (EVA) by NICE is helping Ethypharm to overcome the challenges of conducting an RCT prior to regulatory approval. EVA allows digital interventions to be recommended for NHS use, to collect real-world evidence for a full assessment. In order to be included as a part of the NICE guideline, the digital therapeutics intervention needs to include evidence of effectiveness in the UK IAPT setting.[11] EthyPharm recognised the willingness of NICE and the NHS in engaging with developers to discuss challenges with conducting RCTs, specifically for digital therapeutic interventions for mental health. The potential benefits of introducing mental health digital therapeutics as a treatment option for patients were deemed to outweigh the potential risks. Notably, NICE and NHS England demonstrated an open-minded approach compared to other countries where EthyPharm holds market rights. This positive approach fostered a productive discussion that proved fruitful.

Navigating through the healthcare system can be time-consuming and resource-intensive

Navigating through national health systems, such as the NHS, can be highly complex and challenging, especially for start-up companies. Large pharmaceutical companies are better equipped to overcome these challenges due to their greater resources and extensive networks for understanding the system. Moreover, the NHS has a fragmented structure requiring developers to interact with various local Integrated Care Boards (ICBs) instead of a single national stakeholder to get an intervention adopted into clinical practice.[38]

Lack of training and guidance for healthcare professionals

In addition, training healthcare professionals on how to follow up on and identify suitable patients for new digital therapeutics intervention is a major challenge.[39] Healthcare professionals require substantial

education on the use of digital therapeutics as a treatment option, which can be costly, and the investment is very much dependent on the expected sales of the intervention.

H.5. Lived experience perspectives

The involvement of lived experience experts in the development of deprexis® is not explicitly documented. However, it's noteworthy that both the end user (introduced by the prescriber) and prescriber (introduced by Ethypharm) consulted expressed a highly positive perspective on the implementation of the digital therapeutic intervention in their clinic. Additionally, feedback on the general user experience of the product was favourable.

It was highlighted by the prescriber interviewed that around 73% of patients who were prescribed deprexis® activated the service, which is more than other digital therapeutics interventions across the board (~50%).[xxviii] The activation rate for deprexis® has increased due to improved patient selection by doctors. They now identify patients who are more likely to engage with the digital therapeutic interventions, typically those who have previously benefited from face-to-face counselling. Interestingly, the use of a digital tool was not highlighted as a barrier for older patients. In fact, uptake of deprexis® across various age ranges (currently only prescribed to patients aged 18 and over) has been relatively high.

The end user interviewed appreciate the convenience of receiving treatments at home, particularly on days when the effort to leave the bed and attend face-to-face counselling sessions seems overwhelming. Moreover, the flexibility to engage in exercises at one's own pace and receive daily motivational quotes through texts or emails were highlighted as positive attributes. Patients also welcome that using deprexis® reduces the amount of medications they need to take. Notably, patients place their trust in the product as it was prescribed by their doctors/GPs rather than 'finding' it online or in the app store like most other digital interventions.

While deprexis® offers numerous advantages, the end user interviewed feels there is room for improvement from an end-user perspective. The programme concludes after 90 days, leaving patients without access to resources, except for the daily quotes saved in their phones or emails. This can pose a challenge, for those at risk of relapse, requiring them to consult their doctors for a new prescription. To address this, one end user has suggested that an additional questionnaire be sent to patients after six months or a year to monitor their progress and determine if a new deprexis® treatment course is necessary. This approach aims to streamline the process, reducing the need for patients to initiate the entire prescription process anew. Furthermore, interviewees suggested

[xxviii] Unpublished figure shared by interviewee.

deprexis® would benefit from more diverse representations of ethnic groups or sexualities in the personas used for the scenarios in the exercises. To enhance inclusivity, future products should reflect a broader range of personal journeys.

Ultimately, the inclusion of deprexis® as an NHS-covered treatment option was considered a highly positive development for patients, and there is optimism for its widespread implementation across the entire UK.

> Quote
>
> *"I would highly recommend deprexis®…it can help those who do not seek help due to stigma…it would be good to have the opportunity to say what should be changed and help with the development process…" – An end-user of deprexis®*

H.6. Conclusions

Developers of digital therapeutic products face some key barriers and challenges during the regulatory approval and commercialisation of deprexis®.

The lack of flexibility in RCT design represents a major barrier to the approval of digital therapeutics. However, regulators in the UK, Germany, and the US are actively addressing this challenge by implementing guidelines and accelerated approval processes to assist developers in bringing their products to market. This involves adapting slightly different RCT design compared to the traditional placebo-controlled study. The adjustments include allowing the use of treatment as usual as the control group or incorporating real-world evidence as a part of the assessment criteria.

A challenge for the commercialisation of deprexis® its uptake into clinical practice. This requires the developer to navigate multiple entry points into complex healthcare systems, such as the NHS. In addition, healthcare professionals need to be aware of the intervention and suitably trained for its use.

Finally, interviewees suggested potential improvements for deprexis®, and for digital therapeutics more generally. To enhance inclusivity, developers should take the diversity of users and their experiences into account from the outset, and design the intervention accordingly. According to EthyPharm, the developers of deprexis® (GAIA) are not looking to further develop or improve the product. Unfortunately, the reason for this is unclear.

H.7. Sources

Interviews:

Role	Organisation name	Date of interview
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GP Partner, Clinical Director of Primary Care Warwickshire GP Federation	The Grange Medical Centre; Primary Care Warwickshire	20.10.2023
PWLE/End-user	-	02.11.2023

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Appendix I Case Study (digital devices): Woebot Health

I.1. Summary

Woebot Health	
Type of intervention	Digital
Barrier(s) encountered	Healthcare professional attitudes and perceptions Lack of real-world data (digital)

Woebot is an automated conversational agent (chatbot) delivered to patients on a smartphone. It is designed to provide support and resources for individuals dealing with a range of mental health challenges, such as stress, anxiety, and depression. It uses principles from cognitive behavioural therapy (CBT), interpersonal psychotherapy (IPT) and dialectic behavioural therapy (DBT) to deliver therapeutic interventions. In various studies, Woebot has demonstrated to be a feasible and engaging relational agent to improve users' mental health conditions. There are currently three distinct solutions on the market: Woebot for Adults, Woebot for Adolescents, and Woebot for Maternal Health. The latter is the first digital therapeutics designed to reduce the burden of postpartum depression and it has been granted a Breakthrough Device Designation by the US FDA. Woebot solutions have however not been evaluated, cleared or approved by the US FDA.

Key success factors for developing Woebot include the engagement of a diverse group of experts, such as clinical psychologists, conversational writers and software developers, and people with lived experience. Woebot Health has secured capital from multiple investors, amounting to a total investment of $123.5 million to date.

Woebot Health has been conducting several clinical trials for their interventions, both non-randomised open label studies and double-blind, randomised control trials (RCT). Woebot Health noted that generation of evidence on effectiveness under traditional RCT conditions is challenging as these do not align well with real-world scenarios. Another challenge is to reach patients in the heterogeneous landscape of healthcare providers and associated health systems in the USA, impeding smooth market entry for the developer. However, due to their partnerships with PayrollPlans and with Virtua Health, the company has now access to millions of potential users.

Woebot interventions are currently offered to patients through a non-prescription access pathway. Woebot Health distribute their products to patients in the USA via partner organisations, such as virtual primary care companies, payers and integrated delivery networks. As of September 2023, nearly 1.5 million people have downloaded Woebot.

As next steps, the company is exploring two routes to expand access to patients: (i) tackling new conditions such as individuals struggling with substance use; and (ii) focusing on a fast-growing non-prescription pathway while being open towards a prescription pathway in the future.

I.2. Introduction

Mental health and severe mental disorders are one of the most pressing global challenges of our time.[1,2,3] Over four in 10 adults living with mental health conditions do not receive any care in the United States (US).[4] To systematically address the gap between mental health challenges and mental healthcare, it needs large-scale, high-quality, safe, and accessible mental health care solutions. In this context, Artificial Intelligence (AI) can play a crucial role[5] as digital technologies have the potential to transform mental healthcare in multiple ways. Evidence shows that AI-based conversational agents can help users cope with their mental health challenges.[6] Specifically, mental health apps have the potential

to support individuals who struggle with anxiety and depression.[7] Furthermore, AI can facilitate the collection of data-driven evidence,[8] the development of personalised treatment, and the early detection of mental health conditions.[9,10]

Woebot Health was founded in 2017 by Dr Alison Darcy in response to the mental health crisis in the US and the need to address several key issues and challenges in the field of mental health, including accessibility, scalability, early intervention, and collection of data-driven insights to aid further research in mental health. Through its AI-powered platform Woebot, the company aims to provide scalable, supportive healthcare that enhances participants' coping mechanisms in challenging situations, combining evidence-based and effective therapy principles with an automated and user-friendly digital design.[11,12]

Specifically, Woebot aims to support individuals who struggle with stress, anxiety and (post-partum) depression. As an automated coach, it incorporates principles from cognitive behavioural therapy (CBT), interpersonal psychotherapy (IPT) and dialectic behavioural therapy (DBT). In the design process, the company not only focused on evidence-based therapeutic principles but also aimed at creating a user-friendly solution by involving people with lived experience. The interaction with Woebot is designed to feel less as a 'homework' and more like an engaging, accessible conversation, enhancing users' adherence to the intervention and thus contributing to their improved well-being.[11] Other studies have also demonstrated that a conversational agent improves adherence.[13] The interaction with users is focused on two major activities: mood tracking and online learning. Woebot has employed AI-based natural language processing to understand users' text messages and to decide which expert-designed interventions are most beneficial in the individual case. For this reason, Woebot offers expert content without requiring an active expert, which helps to increase the desired scalability.[11,12,14] The company notes that their tool promotes good mental health practice rather than a digital therapy per se and is able to support users of all ages and genders across different countries. Woebot Health also acknowledges that their chatbot should not replace face-to-face therapy but that both approaches are needed to address the increasing healthcare demand.[15]

Currently, there are three solutions on the market: Woebot for Adults, Woebot for Adolescents, and Woebot for Maternal Health. Woebot is a non-prescription software as a medical device under FDA enforcement discretion; it is currently not evaluated, cleared or approved by the US FDA.[16–18] In order to distribute their product, Woebot Health partners with virtual primary care companies, payers and integrated delivery networks (IDNs, i.e. coordinated systems of healthcare providers and organisations working together to improve the coordination and delivery of healthcare services).[12] As of September 2023, nearly 1.5 million people have downloaded Woebot.[19]

I.3. Development Story

I.3.1. Development story and core principles

The creation of Woebot was a collaborative effort involving a diverse group of experts, such as clinical psychologists, conversational writers, software developers, and people with lived experience. Dr Alison Darcy, president of Woebot Health, was working as a clinical research psychologist at Stanford University where she gained expertise in digital treatment development before founding Woebot Health.[11,12] She and her team of around ten employees, had developed a deep understanding of the mental health context in the US and insights into the supportive potential of digital and AI-based tools during the conception phase.

The development of Woebot started with the vision to provide a high-quality and scalable health care tool, targeted to individuals who need mental health support but are at the same time unable to see a therapist (due to low availability of therapists, anxiety, or stigma, etc.). In 2017, the development of a mental health-centred chatbot was among the first developed chat interventions as most digital mental health tools at that time were simply a less engaging versions of a therapeutic manual in the form of an app.

Since the creation of Woebot Health, the company conducted various studies demonstrating evidence regarding the feasibility and acceptability of Woebot for multiple target groups and mental health challenges.[20–24] To date, according to information provided directly by Woebot Health, the company has conducted 14 RCTs, 2 non-randomised, single-arm trials and an IRB approved study to test generative AI capabilities in mental health.[25] For example, one randomised controlled trial (RCT) showed that young adults reported a greater reduction in depressive symptoms when they used Woebot, while those in the information-only control group did not (N = 70).[20] Participants also reported that they had established a substantial bond with Woebot after three to five days which was comparable to the bond reported for in-person, outpatient, individual CBT and group CBT.[26]

Moreover, Woebot Health included landscape analyses, user research, and stakeholder engagement for the development of its interventions and the subsequent configurations.[27,28] User feedback on the design of the programme was regularly addressed: for example, when users experienced difficulties when faced with a variety of self-help content, a simple decision-making support in the form of guided, step-by-step questions for the users was implemented.

During the COVID-19 pandemic, Woebot Health's engineers and conversational writers developed a Coronavirus programme, which was launched in March 2020 and specifically designed to address the fears and worries related to the pandemic. Thus, Woebot Health was able to swiftly react to the global crisis, which particularly challenged users' mental health and well-being.[29]

In 2021, Woebot Health also received a US Food and Drug Administration

(FDA) Breakthrough Device Designation

[xxix] for their product WB001, a version of Woebot specifically designed for the treatment of post-partum depression.[30] With this, the company reached a major milestone as it was their first product to be granted Breakthrough Device Designation.

Overall, Woebot Health's development strategy is guided by the following principles:

- **Close collaboration with clinical and translational scientists:** An interview with Woebot Health emphasised the focus on the translation from research and knowledge into practicable improvements for individuals' healthcare reality. For this purpose, the company collaborates with clinical and translational scientists to identify issues with availability of and access to mental health treatment.
- **User safety:** Safety represents a priority for Woebot Health. Woebot can use established protocols in high-risk situations and is HIPAA-compliant (Health Insurance Portability and Accountability Act). Users are never confronted with AI-generated content but only messages that are written by clinical experts. Woebot Health continuously aims to improve their products' safety and effectiveness. For this purpose, the company has created a Scientific Advisory Board.
- **Continuous learning and improvement of the product:** Woebot Health regularly conducts studies and user research to gain insights into how to improve their products. The company has recently started a new RCT to analyse the way Large Language Models can help provide more potent and engaging interactions for participants. These insights will then be expected to be used to improve their products. [28,31,32]
- **Broad spectrum of target groups:** Woebot Health targets a wide range of potential users with diverse mental health challenges to reduce the overall burden of mental health. Maximising inclusion was highlighted in the interview as an important principle. Woebot is currently available for adults, adolescents, and new mothers. In addition, the company is currently conducting research to establish a Woebot design for individuals struggling with substance use (Woebot for Substance Use Disorders, W-SUD); a first RCT showed that W-SUD significantly reduced substance use occasions, more than the waitlist control.

[xxix] The Breakthrough Devices Programme provides patients and health care providers with timely access to medical devices by speeding up development, assessment, and review for e.g. premarket approval. Breakthrough Devices must meet the FDA's standards for device safety and effectiveness in order to be authorised for marketing. The Breakthrough Devices Programme offers manufacturers an opportunity to interact with FDA experts through several different programme options to efficiently address topics as they arise during the premarket review phase. See: https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program

I.3.2. Challenges

Woebot Health has been confronted with several challenges in developing and deploying their digital tool.[28] The interviewed employee stresses the difficulty of proving the effectiveness of their products through traditional RCTs: RCT samples often do not accurately represent the broader real-world population. There is an inherent trade-off between the control required by RCTs and the need for real-world applicability, creating a substantial challenge in the industry. It is thus vital not to rely solely on RCT results, as real-world product usage testing is equally important. The interviewee considers a combined approach that entails both learning from real-world user experiences and generating evidence through RCTs a better alternative. In the literature, the issue of external validity in RCTs, i.e. the challenges in applying RCT results to diverse real-world populations due to the rigid inclusion criteria of RCTs, is also highlighted. [33,34] In direct correspondence with Woebot Health, the company pointed out that the conducted RCTs as well as the additional non-randomised, single-arm trials and studies do focus on generating real-world evidence, regardless of format.

General research control challenges were highlighted, such as defining suitable placebo alternatives and establishing realistic benchmarks for the effectiveness of digital mental health tools and devices.[35] Particularly, Woebot Health considers it is important to evaluate whether the digital tool is better than no treatment at all, rather than comparing it to existing applications and alternative treatment options, considering that many users do not see a therapist or receive any kind of validated support.[28]

Simultaneously, Woebot Health is facing challenges in getting their products into the market due to the diversity of clinical providers and systems in the US. For instance, CBT may not be suitable solutions according to all clinical actors. Healthcare professionals unfamiliar with AI-based digital interventions would need to be educated to recognise the value of the product and prescribe it for patients. These complexities make 'gated' market entry a demanding task for the company. However, due to their partnerships with PayrollPlans and with Virtua Health in 2023, the company has now access to millions of potential users.

Exploring both a prescription and non-prescription pathway is not without challenges: Woebot Health has just decided to pause the prescription trial for WB001. Today, the company is observing a growing demand for digital behavioural health solutions, while the prescription pathway is taking longer to mature. According to the interviewee, the FDA processes to authorise software as a medical device are not optimal as processes are historically targeted towards the evaluation of pharmaceuticals. External studies also demonstrate that the FDA's regulation of medical software is inconsistent and controversial, due to the rapid technological progress that have outpaced the FDA regulatory processes.[36,37] Consequently, they decided to pause the trial to concentrate resources where they

foresee the most immediate impact. They anticipate that prescription digital therapeutics will play an important role in the future, which is why they will observe how the FDA regulatory framework will develop. In the meantime, Woebot Health continues to drive evidence and compliance in their current non-prescription solution of Woebot.

Currently, Woebot interventions are available as a non-prescription device in order to reach as many users as possible.[27] While the non-prescription pathway may offer flexibility, rapid market entry, and reduced regulatory burden and cost, it also limits market credibility and reimbursement opportunities.

I.3.3. Partners and collaborations

Woebot Health raised $90 million from venture capital firms New Enterprise Associates (NEA) and Jazz Venture Partners L.P. – with participation from funds and accounts managed by BlackRock Private Equity Partners and Owl Ventures – in 2021, amounting to a total investment of, according to Woebot Health's direct insights, $123.5 million for the company as of today.[25]

The company also fosters several partnerships to distribute their product. In September 2023, Woebot Health announced a partnership with PayrollPlans and Curai Health with the aim of giving employers the possibility to provide their employees with accessible, high-quality, and affordable mental health services.[38] Additionally, in October 2023, another collaboration with Virtua Health, South Jersey's largest healthcare provider, was disclosed that would allow primary care specialists to offer Woebot for adults as a clinically supervised complementary resource for individuals in need of support while waiting for behavioural therapy or seeking alternatives to conventional in-person therapy sessions.[39–41] With these collaborations, ('gated non-prescription pathway') Woebot Health aims to distribute their tools via plac as credible multipliers in the field.

I.4. Conclusions

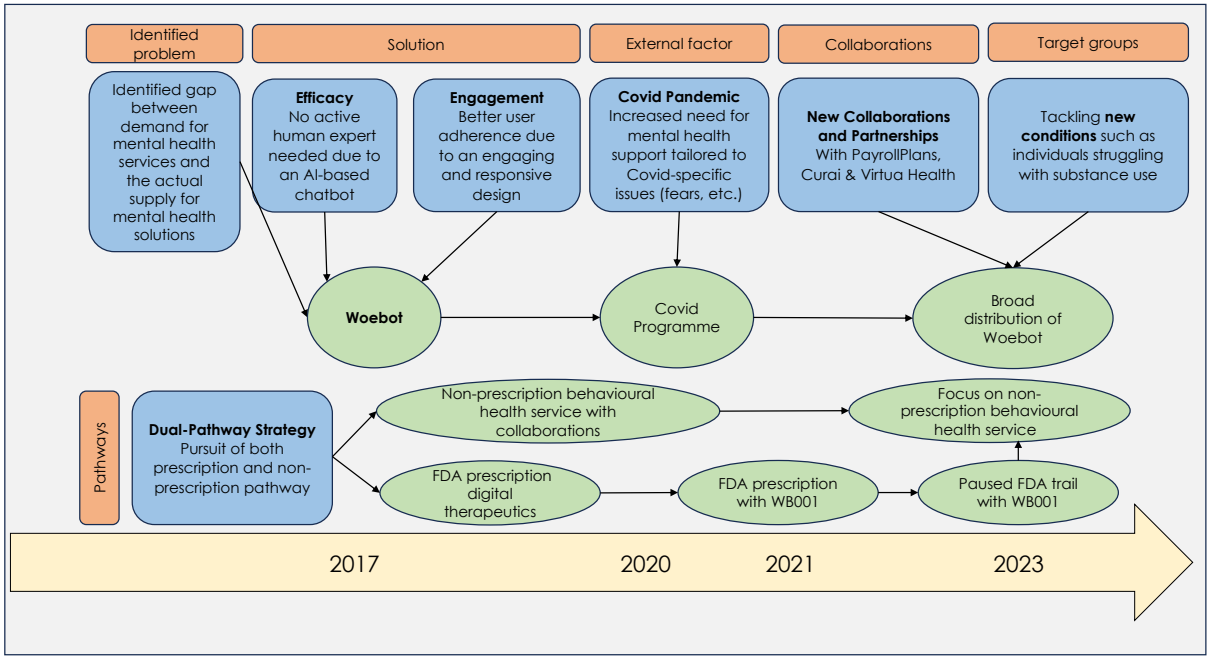
Woebot Health's journey began with a vision to provide accessible, high-quality and safe mental health support to individuals in order to decrease the burden of mental health challenges on a global scale. Their approach blends evidence-based principles with user-friendly design, utilising AI-driven real-time text-based conversations. By September 2023, nearly 1.5 million people have downloaded Woebot.[19] Their success to date has been enabled by venture capital investment of over $120 million and a number of partnerships with various healthcare actors to help to distribute the product.

According to the interviewee, digital interventions and therapies will continue to be developed and used as evidence suggests that these can be as effective as conventional medications but with fewer side effects.

As next steps, the company is exploring two routes to expand access to patient cohorts: (i) tackling new conditions as new use cases for their product such as targeting individuals struggling with substance use; and (ii) while currently focusing on non-prescription pathways for their products, exploring prescription

pathways and reimbursement options
in the longer term.

I.5. Visual: Developer decision-making pathways with a timeline



I.6. Sources

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Role	Organisation name	Date of interview
Vice President, Translational Science at Woebot	Woebot Health	06/10/2023

Feedback via E-Mail:

Role	Organisation name	Date of correspondence
Vice President, Corporate Communications	Woebot Health	19/12/2023

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Appendix J Case Study (non-digital devices): Digital Pill

J.1. Summary

Digital Pill	
Type of intervention	Medical devices: TMS
Barrier(s) encountered	Ensuring the sufficiency of funds to keep operations while navigating regulatory trials (Overcomes treatment adherence challenges particularly in relation to frequenting clinics for it)
The Digital Pill is an implantable medical device for the treatment of depression, under development by the US start-up company Inner Cosmos. It is based on the principle of an existing treatment method, Transcranial Magnetic Stimulation (TMS), which uses electromagnetic pulses on targeted areas of the brain. To resolve existing issues with patient access and adherence to treatment, Inner Cosmos is developing the Digital Pill to administer TMS via an implantable device rather than as a procedure at a health facility. The device is expected to benefit from building on an existing approach which has been approved for use and has been widely offered for the treatment of depression in the United States. The main concern for the developers is the sustainability of funding throughout the development pathway until commercialisation.	

J.2. Introduction

Approximately 280 million people globally live with depression.[1] One of the main barriers in addressing this care need is poor adherence to treatment.[2,3,4] Reasons include that many people suffering from depression lack the resources to afford treatment, are unable to frequently visit facilities where treatment is delivered, medication fatigue, or simply forget to take the prescribed medication.[5]

One approach to treating depression is via neuromodulation, in which a device applies targeted electrical or chemical stimulation to specific areas of the brain, with the aim of modulating or altering neural activity.[6] Neuromodulation therapies include transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), and vagal nerve stimulation (VNS), all of which have shown promising results across a range of neurological and neuropsychiatric disorders.

In TMS, an electromagnetic coil is placed on the surface of the scalp to deliver pulses that stimulate nerve cells in a targeted area of the brain.[7] The approach was originally investigated for the treatment of movement diseases, but researchers discovered serendipitously that TMS also affected symptoms of mood disorders.[8] Following a large industry-sponsored trial published in 2007, TMS treatment has been available in the United States since 2008.[9,10] Since then, evidence from more than 35 randomised, sham-controlled trials confirms that TMS is an effective treatment for depression and suggests that it produces fewer side effects compared to other treatment approaches.[3] However, TMS typically requires patients to visit healthcare facilities for five sessions

per week over the course of four to six weeks, requiring substantial time commitment from patients and healthcare practitioners.[11,12] Especially since many individuals with depression face challenges in maintaining motivation, this can reduce treatment adherence.

A US-based start-up, Inner Cosmos, is currently developing a neuromodulation system - the Digital Pill - that solves this problem. The Digital Pill is an implanted Brain-to-Computer Interface (BCI) device of approximately 20 mm in diameter that can be operated in remote collaboration between the patient and a practitioner, thus reducing the time required of both.[13] The device is implanted under the scalp and on the skull, without direct contact with the brain, and uses electrodes to micro-stimulate neural networks.[13] Unlike other systems using neuromodulation, implantation of the Digital Pill is minimally invasive and does not require open brain surgery. Once in place, the implant is paired with a 'pod' placed on the skin over the device which acts as a power source and records data on brain activity during treatment. Based on the patient's brain activity. The data is shared with the healthcare practitioner to monitor the patient's progress and allows the system to tailor the stimulation protocol to the needs of the individual.[6]

J.3. Development Story

Inner Cosmos' co-founder and CEO Meron Gribetz was motivated by his own experience with pharmacological interventions to ADHD. Suffering from side effects because of the ADHD medication, Gribetz turned to think about mental health interventions which target only specific parts of the brain, leaving other parts unaffected. A neuroscientist by training with a background in technology start-ups (as founder and former CEO of a company developing augmented reality headsets),[14] Gribetz decided to engage with clinical experts in laser neurosurgery (Dr Eric Leuthardt), neuropsychiatric BCI (Dr Darin Dougherty), and optogenetics (Dr Ed Boyden). Collectively, the team had extensive experience in entrepreneurship, in using a range of implantable medical devices for psychiatric conditions and in working with patients with treatment-resistant depression (i.e. patients who do not respond to pharmacological treatment).

First, the team considered various treatment approaches, ultimately deciding to focus on transcranial magnetic stimulation (TMS) as the most promising option for treatment of depression with fewer adverse effects than pharmacological treatments.[12] They also envisaged that an implantable device, the Digital Pill, would address current issues with patient adherence, reduce the time required from health practitioners, and improve access to TMS for people suffering from depression.[13]

Gribetz co-founded Inner Cosmos in 2016, which proceeded to secure the IP in the same year.[14,15] The company raised pre-seed funding in July 2020 and US$10m in seed funding in March 2022, from venture capital investors including lool ventures, KittyHawk

Venture Capital and Loup Ventures.[16,17]

To date, Inner Cosmos has managed most of the development in-house.[13] For the development of the physical prototype, the company subcontracted Draper Laboratory, a US-based research and development organisation.[12] In 2022, Inner Cosmos reported that it had received an Investigational Device Exemption (IDE) from the United States Food and Drug Administration (FDA), and was able to start testing the technology in humans.[18,19] The Digital Pill was implanted into the first patient in July 2022 for a 12-month early feasibility study.[20]

Based on learning from the early feasibility trial, the company will iterate and improve on the original design. For example, the device has already evolved to include fewer pieces and be smaller than the prototype implanted in 2022. The team also plans to gather qualitative insights from study participants on their experience, such as the realities of charging the Digital Pill through the skin, sensations while using the product, and optimal stimulation times. Feedback from people with lived experience on the concept of the Digital Pill has already indicated that patients are interested in the device due to its remote operability and the discreteness of the small implant.[13]

At the time of writing (October 2023), Inner Cosmos is in the process of raising another round of seed funding. The company estimates that this will carry it through the feasibility trials stage; additional funding rounds are planned to cover future clinical studies.[13]

J.4. Facilitators and challenges

Going forward, the developers of the Digital Pill need to demonstrate its ability to improve depression, navigating the regulatory landscapes to reach approval and market access.

The Digital Pill is based on TMS, a neuromodulation method that has been shown to be effective in treating depression over many years. Compared to treatment approaches based entirely novel principles, this lowers risk that the Digital Pill will fail to alleviate symptoms in clinical studies. TMS is also routinely reimbursed by most insurers which has given the developers confidence for the future of the Digital Pill.[6]

A major challenge faced by the company is regulatory uncertainty. In the United States, the level of regulatory control depends on the FDA risk classification of the device. On a scale of I-III, class I includes devices with the lowest risk to the patients' health and safety, and Class III those with the highest risk. For example, traditional TMS approaches fall into device class II,[21] while DBS implants received risk classification III.[22] The Digital Pill incorporates features of both approaches: It is a TMS device (class II), but operates as an implant, similar to DBS devices in class III. On the other hand, the Digital Pill is minimally invasive compared to DBS devices which are implanted directly into the brain, lowering the risks associated with the procedure. Hence, as the first

implantable TMS device, the Digital Pill does not fit neatly into an existing category, but can rely on the precedent laid down by DBS.

This brings into focus another challenge: The need to raise sufficient funds to cover development costs and carry the company through the regulatory approval period. The mean cost of Clinical studies for a therapeutic complex medical device in the United States was $32.1m by one estimate. In that, Feasibility studies were assessed to cost approximately $1.4m on average, and Pivotal studies $30.1m.[23]

Ensuring the funds for staffing and contracts through the development and regulatory milestones is a routine consideration in intervention development in the United States. To this end, Inner Cosmos monitors the balance between funding received and the spending on a monthly basis to determine the length of the projected runway. Against this, the team factors in their developmental and regulatory objectives to monitor the financial feasibility of the development process. To support the feasibility of this system for Inner Cosmos and developers generally, the FDA are mandated by United States Congress to respond to applications and queries within fixed timeframes.[6] As such, developers can expect approvals or issues raised at reasonable timeframes which, in turn, minimises inactive waiting times.

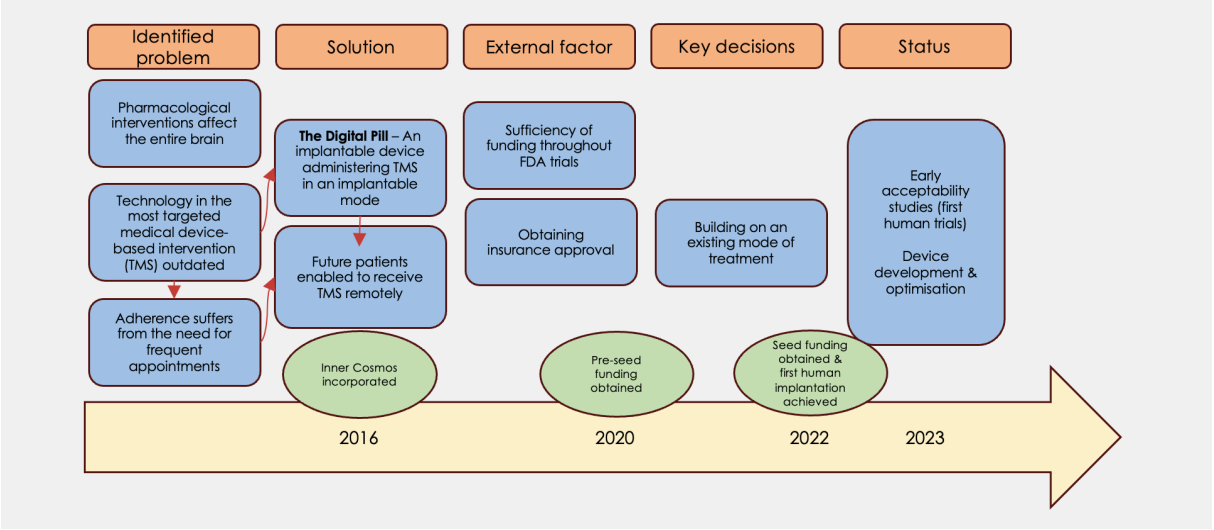
This said, the survival of interventions is entirely dependent on the level of funding acquired by developers across intervention types.

J.5. Conclusions

Inner Cosmos has targeted the development of a device that employs an existing treatment method for depression but delivers it in a novel way to increase patient adherence and access. To date, the company was successful in advancing the Digital Pill from concept to first-in-human studies, securing the necessary IP and funding. The developers are planning to embark on further clinical studies to demonstrate the system's safety and effectiveness and to gather views of PWLE to ensure a user-friendly design.

Going forward, Inner Cosmos has to contend with some considerations: As the first implantable TMS device, the Digital Pill does not fit into an existing FDA device category. The Pill does, however benefit from the precedent set by the likes of DBS to manage the regulatory process successfully. The other element is the sufficiency of the company's projected funds runway to ensure its running while the regulatory phase lasts prior to commercialisation.

J.6. Visual: Developer decision-making pathways with a timeline



J.7. Sources

Interviews:

Role	Organisation name	Date of interview
Associate Professor of Psychiatry	Harvard Medical School	19/10/2023

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Appendix K Case Study (non-digital devices): Fisher Wallace

K.1. Summary

Fisher Wallace Labs - OAK	
Type of intervention	Device (non-invasive)
Barrier(s) encountered	Device parameter testing requirements high Regulation time consuming and resource intensive

Fisher Wallace Labs have been developing a wearable device for Cranial Electrotherapy Stimulation (CES). Building on the success of a first version of the device, the company has been developing Version 2.0, named OAK, for the treatment of depression and other neuropsychiatric and cognitive disorders. The patent-pending technology was designed to be affordable, attractive and user-friendly and is a completely head-worn wearable with integrated electrodes. Rather than having to go to the clinic for treatment, as is the case for other types of brain stimulation therapies, the device is used in the home. Fisher Wallace is also developing a companion app that will be able to track symptoms and cognitive performance, and may integrate other digital health services in the future. In 2023, a 4-week clinical trial demonstrated the safety and effectiveness of OAK for treatment of depression.

A key challenge in the development of this device was a change in classification by the FDA, finalised in 2019, associated with more stringent data requirements. The company is now looking for funding to implement a longer follow-up study required to apply for FDA approval and to commercialise OAK in the US and Europe. Fisher Wallace also faced a challenge securing venture capital, which it partially navigated through a $9m crowdfunding campaign.

K.2. Introduction

Fisher Wallace Labs is a health technology start-up based in New York City, which develops wearable neuromodulation devices for the treatment of depression, anxiety, as well as insomnia, and Alzheimer's Disease.[1] The devices use a type of non-invasive brain stimulation called transcranial alternating current stimulation (tACS), a method which has traditionally been applied in cognitive neuroscience but is more recently being utilised for psychiatric conditions.[2]

The initial device, Version 1.0, was manufactured and sold by Fisher Wallace under the brand name Fisher Wallace Stimulator between 2009 and 2023.[3] The company is currently developing a second version of the device, called OAK.[4]

This case study describes the development of Fisher Wallace's wearable neuromodulation device from the 1990 to today, sets out the key challenges encountered, and outlines the role of PWLE in progressing the wearable towards commercialisation.

K.3. Development Story

K.3.1. Version 1 (Fisher Wallace Cranial Stimulator)

The initial device (then called the LISS Cranial Stimulator) was developed by engineer brothers Drs Saul and Bernard Liss who patented the technology and obtained FDA clearance for the device in 1990.[5] The original founders of Fisher Wallace

Labs, Charles Fisher and Dr Martin Wallace, purchased the intellectual property from the Liss brothers in 2006; Kelly Roman joined as co-founder in 2009 following the death of Martin Wallace.[6] Version 1.0 of the device consists of a handheld pulse generator that connects to two electrodes which are held in place on either side of the patient's head with a Velcro headband. Patients used the device at home, once or twice a day for 20 minutes.[7]

At the time, Cranial Electrotherapy Stimulator (CES) treatment was classified as a pre-amendments Class III device, requiring only a 'simpler' 510(k) FDA clearance rather than a premarket approval application. These two regulatory pathways both aim to ensure that medical devices meet the necessary standards for safety and effectiveness, but differ in their stringency. The premarket approval process is more rigorous and is typically applied to higher-risk devices,[8] while the 510(k) clearance process is a faster pathway used for devices with lower perceived risk that have a comparable counterpart already on the market.[9]

Between 2009 and 2023, Fisher Wallace manufactured and sold a Version 1.0 device under the brand name Fisher Wallace Stimulator, distributing 100,000 units via 14,000 prescribers in the US and Europe, at an average retail price of $400, generating $40 million in revenue.[3] The device was purchased by patients out-of-pocket, except in Maine where Medicaid (MaineCare) approved reimbursement in 2016.[10] In 2015, Fisher Wallace funded a pilot study which demonstrated that the company's device produced a rapid and significant decrease in depression symptoms for patients diagnosed with bipolar II depression.[11] This went beyond the required level of evidence at the time, as the FDA and European notified bodies did not require clinical trial data to validate effectiveness of wearable brain stimulation devices intended to treat depression, and instead only required manufacturers to demonstrate substantial equivalence to previously cleared devices.[12]

The 510(k) FDA clearance for the Version 1 device has now expired[13].

K.3.2. Key regulatory change

In 2011, the FDA began the process of requiring premarket approval for CES devices intended to treat depression, placing them in Class III which requires large scale clinical trial data to validate safety and effectiveness.[12] Fisher Wallace contested the Agency's decision at the time through the filing of a reclassification petition that asserted CES devices should be reclassified into Class II.[14] Ultimately, the FDA finalised its decision to require premarket approval for the treatment of depression in 2019.[15]

While the FDA has not asserted that CES devices pose high risk, the agency has communicated that the risk associated with ineffective treatment is high among depressed patients as they may worsen and become suicidal. As the result, the FDA now requires premarket approval (PMA) for CES devices intended to treat depression, the highest level of medical device regulation.

Regulatory changes have also occurred in Europe, where the requirements for a CE mark were changed from the Medical Devices Directive (MDD) to the more rigorous Medical Device Regulation (MDR).[16]

K.3.3. Version 2 (OAK)

As a result of the FDA's 2011 announcement, Fisher Wallace prepared to meet the new, more stringent, requirements by starting to develop a Version 2.0 wearable, called OAK.[17] In 2019, Fisher Wallace launched its first equity crowdfunding campaign through the platform StartEngine to raise funds for OAK.[18] Approximately 4500 individuals have invested via the platform, including thousands of current users of the Fisher Wallace Stimulator, who collectively now own approximately 15% of the company. Since 2019, the company has raised over $9 million through equity crowdfunding, signalling high customer interest for OAK. In addition, the company received approximately $3 million in investment from SHUFL Capital, a UK-based seed investment firm focused on businesses in the areas of sleep, health, fitness and leisure.[19]

Kelly Roman, CEO of Fisher Wallace, worked with designers from Microsoft and Beats Headphones for two years to develop a wearable with perfected stimulation and form factor (e.g. shape and configuration). The patent-pending technology was designed to be as affordable, attractive and user-friendly as possible and is now a completely head-worn wearable with integrated electrodes. Available in multiple colours, OAK will allow patients to choose the colour of their depression treatment. OAK will also be Bluetooth enabled, with a speaker for voice assistance during use. In addition to the design changes, the newer version has a fixed output, set at the optimal amount of electricity for effectiveness, safety and comfort, compared to the first version that allowed patients and providers to vary the output themselves, within a range of 0-4 mA. Fisher Wallace is also developing a companion app that will be able to track symptoms, as well as cognitive performance. The developers are looking at integrating talk therapy and curate other digital health services through this app, for customers who would benefit from an additional intervention at an affordable price.[20]

To determine the effectiveness of the OAK device, the company has funded several clinical trials. In 2023, Fisher Wallace funded a randomised controlled trial with 255 participants suffering from moderate to severe major depressive disorder, using a research version of OAK.[21] The results of the 4 weeks study indicated that active treatment was significantly more effective than sham (placebo) treatment in reducing depression among patients who were moderately or severely depressed at baseline, as measured by the Beck Depression Inventory, Second Edition (BDI-II)

[xxx]. Starting in the first week of twice-daily use, the treatment reduced depression without causing any serious side effects.[22,23] The article summarizing the results was accepted for publication by The Journal of Clinical Psychiatry in December, 2023. Data from the study will be submitted to EU and UK notified bodies to obtain an initial CE and UKCA Mark for the acute treatment of depression.[24]

Another study funded by Fisher Wallace is a real world evidence study conducted in partnership with the Seattle Police Department and Washington State University in 2022, which investigated the effect of OAK on treating Generalised Anxiety Disorder, insomnia, and stress.[25] The trial enrolled over 200 first responders, a patient population with a high mental health and stress burden. Participation in the study required a diagnosis of Generalized Anxiety Disorder.

OAK has been trademarked in the US and Europe[26,27] and provisional utility and design patents have been filed.[28]

K.3.4. Next steps and outlook

The FDA recently communicated to the Fisher Wallace that a study analysing a longer-duration of treatment, beyond the completed 4-week trial, would be required for approval. The company is now raising capital to conduct a 10-week clinical trial, using a protocol pre-approved by the FDA. Simultaneously, the company is in the process of completing engineering and manufacturing for the commercial version of OAK that will deliver the same Version 2.0 stimulation used by the research devices. Roman reports that Fisher Wallace is planning to gain regulatory approval in both the US and Europe by 2025.

Fisher Wallace projections anticipate that as many as 60,000 of its past 92,000 customers who purchased Version 1.0 will upgrade to OAK, representing more than $30 million in potential revenue at launch. In the longer term, the company believes that holds a strong market position. In addition to patent protection, the more stringent requirements for FDA approval will provide a high barrier to entry – even if a competitor cloned OAK, it would still need to conduct a large scale clinical trial and obtain FDA approval before bringing a product to market for the treatment of depression. Priority has therefore been placed on achieving FDA approval.

K.3.5. Barriers and Challenges

The uncertainty regarding FDA regulation prior to 2019, and the lack of clear scientific evidence of effectiveness prior to the publication of the company's 4-week study, have been significant challenges for Fisher Wallace, limiting the company's ability to raise venture capital until very recently. Medical device technology typically requires tens of millions of dollars of funding to achieve FDA approval, as has been the case with other non-invasive medical devices such as transcranial magnetic

[xxx] The Beck Depression Inventory Second Edition (BDI-II) is a multiple-choice self-report inventory that assesses severity of depression. The minimum score is 0 and the maximum score is 63, with a higher score indicating more severe depressive symptoms.

stimulation (TMS) and electroconvulsive therapy (ECT), so the cost of applying for regulatory approval can be challenging for SMEs. This can be particularly risky when the requirements are unclear, differ between countries, or are subject to change.

The company acknowledged some benefits of the new regulations, as the more stringent rules force developers to undertake more rigorous testing. As mentioned above, while the requirement for robust scientific evidence is challenging for Fisher Wallace, it also presents a barrier to market entry for competitors.

As described above, Fisher Wallace has found it difficult to secure investment from VC funds for their CES device, but the company is optimistic that this will improve once investors gain confidence in the technology's safety and effectiveness, validated by the trial results published in a peer-reviewed journal.

The company explained that clinic-based approaches to brain stimulation, such as TMS, had seen more investment compared to home-based wearables, as clinic-based approaches provide doctors and clinics with revenue sources. However, Fisher Wallace contends that offering its device as a wearable holds the potential to reach a similar in scale to that of smartphone. The company's approach to commercialisation hence combines a consumer approach with a medical device approach. The developer was successful in securing investment through the crowdfunding route. Without this input from the public, the company would not have been able to progress with the development of OAK.

Quote

"The private markets remain challenging for Series A stage medical device companies, but we we've already conducted, thanks to successful equity crowdfunding, substantial clinical research that validates our technology as safe and effective - we've therefore taken a significant amount of the technology and regulatory risk off the table that venture investors often fear."

K.4. Lived experience perspectives

Involvement from people with lived experience (PWLE) of depression and anxiety has been crucial to the continued survival and success of Fisher Wallace. This has been the case from the very beginning of the company, as one of the founders, Dr Martin Wallace, had been suffering from depression following the aftermath of 9/11 and found that the LISS Cranial Stimulator successfully alleviated his low mood. This motivated Wallace along with Charles Fisher, an entrepreneur, to purchase the patents from Liss.[29]

Fisher Wallace refers to themselves as a 'patient-owned healthcare company'

due to the many end users who have invested in the company. The high levels of funding received from the public to assist in the development of OAK is encouraging for the company, as it indicates future commercial success for the product.

The opinions and preferences of potential end users informed the product development phase of OAK. For instance, many people disliked the wires in the original device, so the new product was designed to be wireless. Neuromodulation devices were often described as 'scary looking' and therefore not appealing to a large customer base. The OAK device will be made available in multiple colours to make the product look 'less medical'. The developers also gathered customer feedback and took the opinions of PWLE into account when determining the price point of the product. The company considers the creation of an affordable and accessible intervention important to its mission (and crucial for commercial success).

PWLE was also gathered during clinical trials through collection of qualitative data from participants. Input from PWLE also influenced how the developers determined the primary endpoint of the upcoming 10-week study for FDA approval. The company reported that the endpoint for the 4-week study was originally set after two weeks of receiving the treatments, but after patients self-reported results were being experienced after only one week, the primary end point has now been moved to week one.

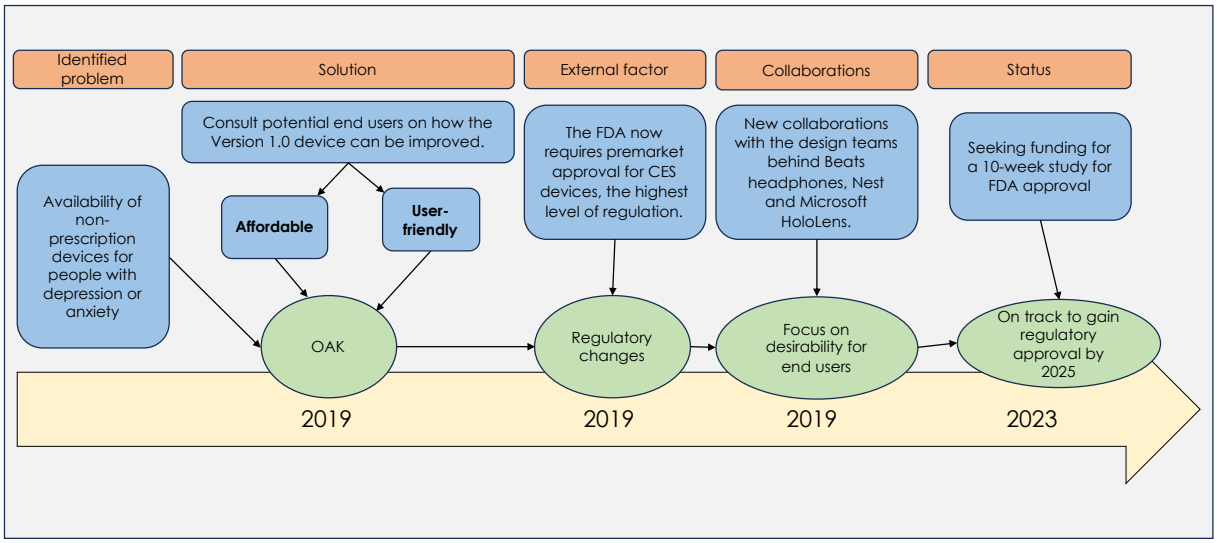
K.5. Conclusions

Fisher Wallace have already successfully brought a wearable tACS neuromodulation device to market and have made progress with developing the successor, OAK. By incorporating the perspectives and feedback of PLWE, the company has improved its existing product to be more user-friendly and appealing. In return, Fisher Wallace was able to raise over US$9 million through public equity crowdfunding. The financial support from Fisher Wallace's customers was therefore an effective solution to the lack of more traditional investments. The company is optimistic that with the completion of the scientific validation phase financed through funding from its customers, it will now be easier to secure venture capital.

The changing requirement of regulatory bodies was the largest challenge faced by Fisher Wallace during the R&D pipeline of the OAK For a smaller company with less capital, it can be very difficult to fund intensive clinical trials, and Fisher Wallace have therefore been in discussions with the FDA for the last 10 years to have CES devices reclassified. On the other hand, the company expects that the more stringent regulations will make OAK more competitive once the product reaches the market.

The developers are currently seeking funding for a 10 week trial to support FDA approval, with sight to complete the regulatory process by 2025.

K.6. Visual: Developer decision-making pathways with a timeline



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Interviews:

Role	Organisation name	Date of interview
Co-Founder, CEO, and Director	Fisher Wallace Labs	05/09/2023

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Appendix L Case Study (pharmaceuticals): Boehringer Ingelheim (BI)

L.1. Summary

Boehringer Ingelheim (BI)	
Type of intervention	Pharmaceuticals (and complementary DTx)
Barrier(s) encountered	Clinical trial recruitment Stigma

Boehringer Ingelheim (BI) is a German pharmaceutical company that has a steadily growing pipeline of drug interventions in their pipeline. BI are currently combining 'precision psychiatry' and a transdiagnostic approach in order to develop effective pharmaceuticals by focusing on the individual variability of mental health conditions rather than being restricted by the traditional single-diagnosis approach.

BI currently have pharmaceutical interventions in their pipeline for the treatment of symptoms relating to Major Depressive Disorder (MDD), PTSD, schizophrenia, and Borderline Personality Disorder (BoPD), as well as complementary digital therapeutics.

Patients with Major Depressive Disorder (MDD), schizophrenia, and Borderline Personality Disorder (BOPD), were found to all share a common abnormality in the amygdala and BI are therefore developing a TRPC4/5 inhibitor to reduce the associated emotional symptoms in all three conditions. If successful, this drug would therefore be able to improve the symptoms of a larger population. However, there have been difficulties in recruitment for clinical trials as the developers ideally only want to include patients with the specific biological abnormality.

BI have also consulted PWLE to determine the mental health symptoms with the most significant day-to-day burden. The majority of people with schizophrenia experience cognitive difficulties, but due to the stigma around the disease, interventions relating to psychosis are prioritised over treatments for other symptoms. BI are therefore developing what would be the first pharmaceutical that reduces these cognitive symptoms in schizophrenia, and would have a significant impact on the quality of life for these individuals. To provide more holistic treatment, BI have partnered with Click Therapeutics to also develop a digital intervention that supports patients in reducing the negative symptoms of schizophrenia.

While the pharmaceutical intervention that BI is developing would meet a clear unmet need, there are also challenges that come with this. Schizophrenia is a condition with high levels of stigma associated with it compared to depression and anxiety, and BI have experienced difficulties in recruitment for clinical trials due to this. They are also concerned about uptake by clinicians in the future, as reducing cognitive difficulties is not seen as a priority. BI developed an immersive pop-up campaign to demonstrate the impact that cognitive symptoms can have on an individual's daily life, in order to improve education and awareness.

L.2. Introduction

Mental health conditions affect a large portion of the population, with nearly 800 million individuals dealing with various disorders, constituting around 10.7% of the world's population.[1]

The official diagnostic manuals used to classify mental health conditions, e.g. the DSM-5 and ICD-10, handle psychopathology and substance use disorders as separate and clear-cut categories.[2] This implies that the diagnoses accurately represent the true nature of the individual and

identify specific types of mental disorders as if they were distinct and well-defined. In simpler terms, the current way mental health conditions are diagnosed suggests that a person either has a specific mental disorder or doesn't, that these disorders are different from each other, and that having one disorder doesn't necessarily mean you're more likely to have another.

Clinical experience and research show that these assumptions are not entirely accurate. Firstly, people experiencing symptoms below the diagnostic threshold can still suffer distress and impairment, and individuals with the same diagnosis can experience varying levels of severity. Hence, mental disorders may have a range not captured by fixed diagnoses, and simplifying a complex set of signs and symptoms into a yes-or-no decision loses valuable information. In addition, the single-diagnosis approach may group individuals that behaviourally and symptomatically present similarly, even though their symptoms stem from different biological causes. Secondly, individuals commonly suffer from more than one disorder (which may have overlapping symptoms) and are likely to meet the criteria for additional disorders at rates higher than expected based on individual disorder prevalence. Research examining the dimensions of disorders and their co-occurrence indicates that many mental health issues stem from a limited set of fundamental underlying aspects, i.e. that they may share certain fundamental factors or dimensions. However, the understanding of the underlying causes of mental health disorders is still limited.

The realisation that a one-size-fits-all approach is inadequate for research and to guide clinical care because people differ in ways that are not captured by broad diagnostic categories, researchers are turning their attention to “precision psychiatry”.[3,4] Precision psychiatry aims to develop more effective and tailored treatments by taking individual variability into account, including physiology, environment, lifestyle, genetics, and individual preferences.

This shift towards precision psychiatry has been supported by developments such as the US National Institute of Mental Health Research Domain Criteria (RDoC), a project initiated in 2010.[5] It provides researchers with a “transdiagnostic” framework to study neurobiological mechanisms that may cut across boundaries set by current diagnostic classification systems. The transdiagnostic approach hence focuses on understanding the shared neurobiological mechanisms that underlie psychiatric conditions, rather than on diagnoses based on observable symptoms.[6] The transdiagnostic approach has gained traction over the last ten years, exemplified by a more than tenfold increase in research publications listed on PubMed that include the term in the title (from 95 in 2013 to 1010 in 2023).7

Boehringer Ingelheim (BI) is a family-owned pharmaceutical company headquartered in Germany.8 A relative newcomer to the area of mental health therapies,9 the company is currently

developing pharmacological and digital therapeutics for the treatment of Major Depressive Disorder (MDD), PTSD, schizophrenia, and Borderline Personality Disorder (BoPD). [10]

L.3. Development Story

Boehringer Ingelheim (BI) is taking a holistic and integrated approach to mental health therapy by combining precision psychiatry, a transdiagnostic approach, and the development of non-pharmacological tools - such as digital therapeutics – to be offered alongside pharmacological interventions.[10,11]

The company is currently testing three compounds in clinical trials to treat major depressive disorder (MDD), schizophrenia, post-traumatic stress disorder (PTSD) and borderline personality disorder (BoPD), and has a pipeline of more than 20 in preclinical development.[10] In addition, BI is developing digital therapeutics to be used in parallel with pharmaceutical options for the treatment of schizophrenia.

L.3.1. Precision psychiatry

As described in section A.1, the traditional single-diagnosis approach groups individuals who exhibit similar behavioural and symptomatic patterns, even though their symptoms may stem from different biological causes. Rather than targeting a heterogeneous group of patients with the same DSM-5 diagnosis, BI aims to develop more effective treatments for patient sub-groups that share a specific symptom dimension and underlying neurobiological processes[12]. This stratification of DSM-5 patient groups into sub-groups takes into account individuals' differences in physiology, environment, lifestyle, genetics, and individual preferences and aims to identify more homogenous subpopulations that are more likely to respond to the mechanism of action of a given medication.

Precision psychiatry involves the analysis of large complex datasets to identify differences between individuals in a single patient group and underlying neurobiological mechanisms. Digital phenotyping refers to moment-by-moment data collection from personal digital devices to better quantify the human phenotype, i.e. an individual's observable characteristics, traits, and behaviours.[13]

BI is following three main approaches for digital phenotyping:[14]

- Collection and/or analysis of complex patient data sets on patients' behaviour and attitudes, which can be analysed to better understand mental illness symptoms
- Development of artificial intelligence tools to analyse and interpret the data, which can result in faster and more accurate decision-making across the patient journey
- Deployment of smart devices and sensors in research to measure people's real-time physiological and behavioural data, enhance the range of data collected, and thus enable further insight and understanding

Current BI research projects include a partnership initiated in 2021 with King's College London, which focuses on understanding the neurobiological processes leading to impaired cognition in MDD and schizophrenia.[15] The research involves four clinical studies in both home environments and study centres gathering data from cognitive tasks, neuroimaging techniques, patient functioning assessment through virtual reality tools and digital biomarkers to monitor speech and sleep habits.[16] The studies aim to link specific symptoms to the underlying brain circuit dysfunction, which can inform therapy development. In addition, the research may lead to the identification of novel biomarkers of cognitive deterioration in MDD and schizophrenia.

L.3.2. Pharmaceutical pipeline

Using the transdiagnostic approach described in section A.1, BI is looking to develop solutions that target symptoms that are shared across mental health indications, indicating a common underlying neurobiological process, i.e. focusing on the 'issue' rather than the 'diagnosis'. This raises the possibility of treating individuals suffering from various mental health conditions. Illustrating this approach, a TRPC4/5 inhibitor known as BI 1358894, is currently in Phase II clinical trials funded by BI to test its effectiveness in reducing emotional symptoms in BoPD,[17] PTSD,[18] and MDD.[19] Meta-analyses of neuroimaging studies concluded that a subset of patients within each disorder may share a common irregularity in emotional processing and the amygdala.[20–22] BI 1358894 blocks a target in the brain that has been shown to play an essential role in amygdala function and fear-related behaviour, and may hence treat the overwhelming uncontrolled emotions experienced by people living with BoPD, PTSD, and MDD.[23,24]

Another example of a drug currently under development by BI is iclepertin (BI 425809), a selective glycine transporter 1 (GlyT1) inhibitor that targets cognitive impairment associated with schizophrenia (CIAS).[25,26] Current standard-of-care for schizophrenia centres on antipsychotic medications to relieve symptoms such as hallucinations, disorganised speech and behaviour agitation ('positive symptoms'). However, patients also experience symptoms such as CIAS and 'negative symptoms (decreased motivation, problems with socialisation, and the inability to experience joy) for which there are currently no pharmacological interventions. These cognitive and negative symptoms are common, with 80% of patients suffering from CIAS [25] and up to 60% of schizophrenia patients experiencing clinically relevant negative symptoms that require treatment.[27] As cognitive symptoms include difficulties with problem solving, attention, and memory, they have a significant effect on the patients' ability to independently complete basic daily tasks. [25]

In 2021, BI reported the results of a Phase II trial of iclepertin which demonstrated the drug to be safe and to improve cognition in schizophrenia patients.[28] Based on this trial – and the unmet medical need it could address - iclepertin was granted Breakthrough

Therapy Designation by the US Food and Drug Administration (FDA) to help expedite its development and regulatory review.[29] BI is currently conducting three international Phase III studies to confirm that iclepertin is safe and effective.[30] If successful, iclepertin could become the first approved pharmacotherapy used to treat CIAS.

L.3.3. Complementary Digital Therapeutics

In addition to traditional pharmaceutical interventions, BI is looking to provide patients with a wider spectrum of support to further improve outcomes.

For schizophrenia, psychosocial therapies can help alleviate negative symptoms and increase patients' quality of life, but access for those living with schizophrenia can be limited. Digital therapeutics are more easily available and may enhance the efficacy of pharmacological interventions.[14]

In 2020, BI initiated a collaboration with Click Therapeutics,[31] a company specialising in digital therapeutics, to develop a prescription digital therapeutic for the treatment of negative symptoms of schizophrenia (see above).[32,33] The intervention, referred to as CT-155, is intended to be used in parallel with the pharmaceutical options, such as BI's iclepertin, as part of a holistic treatment plan. CT-155 is a mobile app designed to encourage patients to adjust their behaviour using cognitive and neurobehavioral mechanisms, with the aim of reducing cognitive deficits and improving social functioning.[34] CT-155 is currently being tested in a Phase III clinical trial against standard of care therapy for the treatment of experiential negative symptoms of schizophrenia in late adolescents and adults. [35] In January 2024, the app received Breakthrough Device designation from the FDA, setting it on a path to accelerated assessment and regulatory review.[36]

L.3.4. Barriers and Challenges

BI has encountered several challenges to the development of their innovations.

Misalignment between diagnostic criteria and underlying neurobiology: BI highlighted that the current classification of mental health conditions based on the DSM or ICD can be problematic and present a barrier to development. As described in section A.1, diagnoses of mental health disorders are currently based on observable symptoms which often overlap across diagnoses and do not take into account the underlying neurobiological processes (which may be shared between disorders). Hence, the heterogeneity within any particular patient group is large. In drug discovery, however, a clear and precise understanding of a disease's underlying mechanisms is the starting point for developing new therapeutic concepts, forming the basis for subsequent research projects.[37] In subsequent clinical development, drug candidates are tested with patient groups diagnosed observable symptoms rather than disease mechanism. This misalignment is likely to contribute to the relatively high failure rate of clinical trials in mental health research. It also presents additional challenges for developers,

as exemplified by BI's transdiagnostic approach in developing the TRPC4/5 inhibitor:

Firstly, the target of the drug, frontal amygdala dysfunction, is a mechanism and hence not recognised as a 'disorder' by regulatory authorities. Consequently, regulatory expectations require that TRPC4/5's efficacy is demonstrated in clinical trials for two or three disorders before considering a broader label. This requirement extends the development pathway for BI as multiple programmes have to be implemented, with the associated costs and risks.

Secondly, not all patients diagnosed with BoPD, PTSD or MDD manifest frontal amygdala dysfunction and there is currently an absence of tools to stratify these populations based on biological differences and precisely target patients suitable for participation in the clinical trials. For testing its TRPC 4/5 inhibitor candidate BI 1358894, the developers describe facing two choices: either slowing down the project to determine a way to stratify patients or moving at risk. In this case, BI decided to move forward at risk, selecting trial participants based on questionnaires on specific symptoms or the efficacy of existing medications, rather than biological differences. The company anticipates that the large sample of patients participating in the trial will include a sufficient number of individuals with frontal amygdala dysfunction to demonstrate a positive outcome.

To address these challenges, BI suggest:

- a new classification system based on the neurobiology underlying mental health conditions
- the development of a new clinical toolbox to subtype patients and measure biological end-points

Stigma around schizophrenia and low awareness of the spectrum of symptoms: Another challenge for BI's clinical research is the stigma surrounding mental health, which has had an impact on clinical recruitment. Schizophrenia is particularly stigmatised compared to other mental health conditions such as anxiety and depression.[38–40] As a result, individuals living with schizophrenia may avoid treatment and be reluctant to participate in clinical trials. Potential trial participants may also fear the unwanted side effects of pharmaceutical interventions being tested.

In addition, BI noted that healthcare professionals tend to focus on treating the positive symptoms of schizophrenia (e.g. psychosis). While there is consensus that the disorder also causes significant cognitive impairment and negative symptoms, only some healthcare providers record these issues and few prescribe cognitive behavioural therapy to treat them. If successful in clinical trials, BI's iclepertin would be the first pharmacological intervention to treat cognitive impairment in schizophrenia patients. Once on the market, BI foresee challenges in making iclepertin accessible to patients, given that awareness and treatment of cognitive impairment symptoms lag far behind

those of positive symptoms in clinical practice.

To address these issues, BI suggest training for mental health clinicians to understand neuroscience systems and routinely measure clinical markers of not only schizophrenia but mental health conditions in general. The company has also developed an immersive pop-up campaign to demonstrate the impact that cognitive difficulties can have on an individual's daily life.[41] The campaign aims to improve public awareness and understanding of the whole spectrum of schizophrenia symptoms.

Unclear regulatory pathway for digital therapeutics (resolved): In the early stages of creating the complementary digital therapeutic CT-155, BI faced challenges collaborating with regulatory bodies like the FDA and EMA as the appropriate pathways for digital interventions were unclear at that time. However, this was resolved when the agencies' regulatory approaches solidified. Going forward, BI noted the benefits of developing digital therapeutics: a shorter timeline from concept to market of only 4-5 years compared to 15-20 years for pharmaceutics, and a more streamlined and rapid process for refining a digital product if any issues are identified.

Quote

"*We really think there could be a huge step change in the treatment of mental health conditions by starting to think about the patient biologically rather than trying to think about the patient in terms of the psychiatrists' framework of describing them.*" - BI drug developer

L.4. Lived Experience Perspectives

BI reported in an interview that their approach to developing mental health interventions always starts with the patient. The company consults with PWLE and carers on aspects such as which symptoms interfere most with their day-to-day life, and which type of improvements they would most like to see in their lives (e.g. improving interpersonal relationships, engaging in hobbies, or getting a job). This informs R&D decisions and can help to define trial endpoints that demonstrate to regulators that the therapies are effective.

For example, through discussions with PWLE, BI identified that negative schizophrenia symptoms represented the greatest burden on everyday life for PWLE, information that supported BI's development activity in this area. BI also designed the digital therapeutic in close collaboration with patients, requesting qualitative input on how effective the app is and how it could be improved. BI described that this is an iterative process of improvement which

leads to the creation of an intervention that is best suited to its end users.

BI is also finding ways to increase access to and reduce the burden of participating in clinical trials.[42,43] While hospital-based clinical trials have been the norm, this can be problematic for trial participants, especially for individuals living with mental health disorders. To address this issue, BI implemented the first decentralised clinical trial (DCT) for a trial of its TRPC 4/5 inhibitor in treating MDD. Using digital technology, patients were able to participate from their homes. This not only reduces some of the burdens associated with hospital-based research, but it also facilitates enrolment of a more diverse patient population by reducing geographical bias and enabling those who are unable to leave their homes to participate.

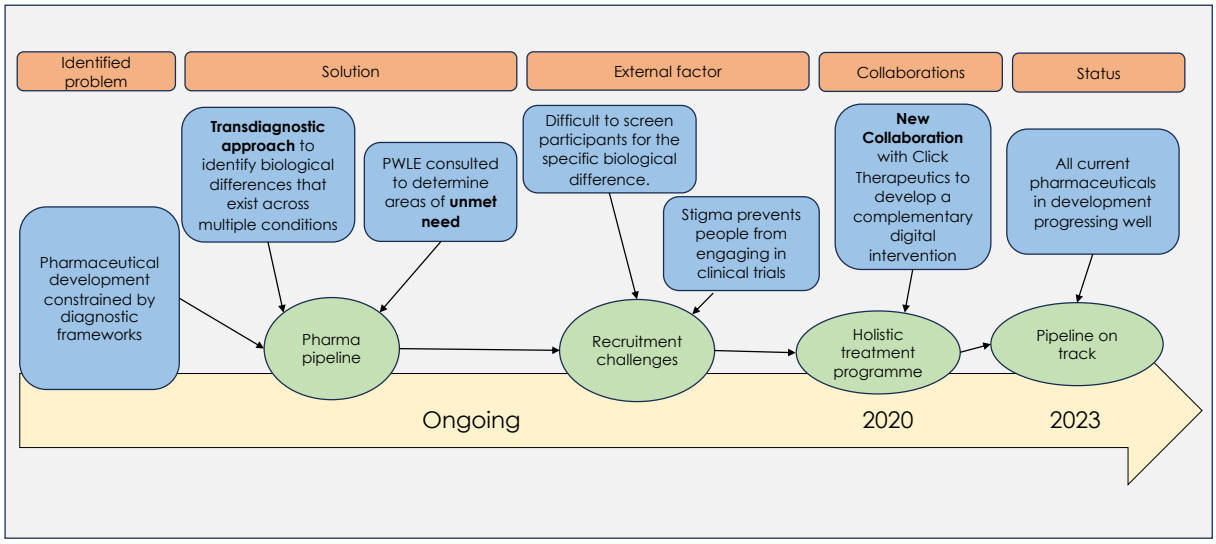
L.5. Conclusions

Many pharmaceutical companies approach the development of interventions by considering all patients with the same mental health condition to have similar symptom profiles which are distinct from other conditions. BI have recognised this to be problematic and is taking an alternative approach which combines 'precision psychiatry', a transdiagnostic framework, and complementary therapeutics in order to develop effective pharmaceuticals.

Two key compounds currently in BI's pharmaceutical pipeline have specifically been developed to alleviate symptoms that will reduce the level of unmet need. The first is a TRPC4/5 inhibitor, which reduces emotional symptoms in BoPD, PTSD, and MDD, and the second is iclepertin, a selective glycine transporter 1 (GlyT1) inhibitor which would be the first drug to target cognitive impairment associated with schizophrenia.

There have been some challenges experienced by the developers associated with the mismatch between the diagnostic criteria and underlying neurobiology, as well as the stigma associated with schizophrenia. However, the TRPC4/5 inhibitor and iclepertin are proceeding well in their Phase II and III clinical trials, respectively.

L.6. Visual: Developer decision-making pathways with a timeline



L.7. Sources

Interviews:

Role	Organisation name	Date of interview
Senior Vice President and Head of Global CNS Diseases	Boehringer Ingelheim	30/06/2023

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Appendix M Case Study (pharmaceuticals): Psychedelics

M.1. Summary

Psychedelics-based treatment for mental health conditions	
Type of analysis	Pharmaceuticals
Barrier(s) encountered	Clinical trial recruitment challenges Clinical trial design challenges: breaking blind Clinical trial delivery: affordability of running clinical trials, resource-intensive and infrastructure-heavy Insufficient public investment in mental health R&D Uncertainty about the return on investment for mental health interventions The stigmatisation of mental health conditions (but more prominently stigmatisation of Schedule 1 substances) Complex and evolving regulations

This case study delves into the use of psychedelics, tracing modern research back to Albert Hofmann's accidental ingestion of LSD in 1943. Despite a promising period in the 1950s and '60s, governmental interventions led to a hiatus. In the last decade, a resurgence in research highlights therapeutic potential, with psilocybin, MDMA, LSD, and ketamine showing promise in mental health treatment. The United States is reforming legislation through a patchwork approach, while regulators in the UK and Germany are actively seeking to address regulatory barriers, South Africa lags in reforming regulatory approval.

A range of challenges to research and clinical use of psychedelics persist. This include:

- A limited understanding of psychedelics' mechanism of action
- Methodological issues raising doubts about internal validity of studies
- Increased patenting activity in the area of psychedelics therapy, potentially limiting innovation in the future
- Regulatory barriers and associated high research costs
- Insufficient mental health infrastructure limiting patient recruitment and patient access
- Persisting stigma and knowledge gaps of psychedelic-assisted therapy

Advocacy groups, exemplified by PsyPAN and Mind Medicine Australia, play a vital role in bridging the gap between researchers and individuals with lived experiences. The study underscores the need for collaborative efforts to explore – and possibly unlock - the therapeutic potential of psychedelics in addressing global mental health challenges.

M.2. Introduction

For thousands of years, indigenous medicinal practices have incorporated psychedelic plants and fungi. Modern psychedelic research traces back to 1938 when Albert Hofmann synthesised lysergic acid diethylamide (LSD-25). In 1943, Hofmann unintentionally became the first person to ingest LSD, setting in motion a series of effects that he initially did not comprehend.[1] The 1950s and '60s witnessed a robust period of scientific and cultural exploration around psychedelics, with evidence

suggesting potential benefits in mental health treatments.[2] However, this momentum came to an abrupt halt in the 1970s and '80s due to governmental interventions that severely impeded global psychedelic research, despite emerging evidence indicating limited medical risks and therapeutic potential. Formally, psychedelics were made illegal under the United Nations 1971 Convention on Psychotropic Substances.[3]

In the past decade, however, research on the potential therapeutic benefits of psychedelics has seen a resurgence. Beyond just basic research into neuropharmacological mechanisms and clinical outcomes, there are strong economic arguments for the therapeutic use of psychedelics. Both substance dependence and mental health disorders, such as anxiety and depression, are increasing in prevalence, placing increased burden on health systems globally.[4] Investments into novel and innovative sources of treatments for mental health and substance use disorders are therefore crucial.

Scientific research has shown promising results across a range of different psychedelic drugs. **Psilocybin**, a naturally occurring compound produced in fungi, has demonstrated efficacy in the treatment of addiction, depression, and end-of-life anxiety.[5] The largest randomised, controlled, double-blind psilocybin study is currently entering Phase III clinical trials in the UK.[6] **MDMA** (3,4-methlyenedioxymethamphetamine) is showing promise in treating post-traumatic stress disorder (PTSD).[7] Clinical trials demonstrated that MDMA-assisted psychotherapy can lead to significant reductions in PTSD symptoms, with some participants experiencing long-lasting benefits.[8] **LSD** (lysergic acid diethylamide) has been studied in the treatment of anxiety, depression, and substance dependence.[9]

Ketamine, while not typically categorised as a psychedelic drug, has played an important role in the resurgence of interest in psychedelics. Ketamine is an illegal drug which, like psychedelics, has also demonstrated positive results in treating mental health conditions. Approval of the use of this drug has lent credibility to the idea of using an illicit substance to treat mental illnesses. It was shown to have rapid antidepressant effects, particularly in individuals with treatment-resistant depression.[10] Approval of the use of this drug has lent credibility to the idea of using an illicit substance to treat mental illnesses.[9]

Given their therapeutic potential, this case study focuses on psychedelics as a treatment for mental health conditions. First, it provides an overall perspective on the status of psychedelic-based treatments and describes the regulatory environment in developments with examples from the US, UK, Germany and South Africa. It then explores several challenges to the research and clinical use of therapeutic psychedelics, and outlines the role of people with lived experience (PWLE) in this area.

M.3. Psychedelics Research and Regulation

Between the late 1950s and early 1970s, numerous research and clinical studies investigated the potential therapeutic effects of psychedelics.[11] These drugs, particularly LSD, were investigated for the treatment of anxiety, depression, and substance abuse disorders. Despite some promising results, these studies included critical methodological limitations, such as a lack of either a placebo or control group, and a lack of standardisation in the monitoring of chosen interventions.[12] Combined with the popularisation of the recreational use of psychedelics, human studies were banned until the early 1990s.

A range of factors underpinned the revival of research on psychedelics. In the US, a Congressional Joint Resolution and a presidential declaration designated the 1990s the 'decade of the brain'.[13] This declaration sought to legitimise research on psychedelics for mental health benefits. Simultaneously, a network of researchers and clinicians across the UK, USA and Switzerland who had strong track records in neuroscience research on drugs continued to press for more research.[14] Historians began publishing accounts of research on psychedelic drugs in the 1950s and 1960s, providing increasing evidence of a societal panic that had caused promising research to be abandoned.[15–17] Taken together, these activities were successful in re-opening discussions on the legitimacy of psychedelic research.

Starting in the mid-1990s, numerous clinical studies demonstrated the therapeutic potential of psychedelics using more robust methodologies. For example:

- A meta-analysis on the use of MDMA for the treatment of PTSD demonstrated a reduction from the baseline of the patient's Clinician-Administered PTSD Scale (CAPS) score[18]
- A pilot study of psilocybin demonstrated the therapeutic benefits for the treatment of anxiety in patients with advanced-stage cancer[19]
- A proof-of-concept study found that psilocybin can be used in the treatment of alcohol dependence, decreasing craving, and increasing abstinence across a 36-week trial, providing a strong rationale for controlled trials with larger sample sizes[20]

The results from these studies highlight the potential of psychedelics to significantly reduce the duration of treatment for depression and anxiety compared to current drug therapies. At present, to treat a patient with a major depressive disorder, doctors typically prescribe a selective serotonin reuptake inhibitor (SSRI). It can take up to 6 weeks to understand whether the drug is working as intended. If it is not, the patient must taper off and try a different SSRI, resulting in a time and resource-intensive process. The research showed that in some cases, patients undergoing psychedelic treatments experienced lasting effects after only one or two treatments given in combination with psychotherapy.[21]

Psychedelics have also been put forward as an alternative to treatment-resistant depression (TRD), commonly defined as a failure to respond to two more treatment courses for different classes of antidepressants.[22] Emerging evidence suggests that psychedelics can have antidepressant effects in patients suffering from TRD, alleviating some of the symptoms including a higher risk of suicide.[23]

M.4. Notable Developments in Psychedelic Research and Legislation

Across the United States, the UK, South Africa, and Germany psychedelics are considered a controlled substance. Based on the specific classification of the drugs (the "Schedule"), government licenses are required for research and clinical use, leading to high costs for their import and storage. Despite these challenges, there are notable recent developments in both regulation and research, as highlighted in the country profiles below.

M.4.1. The United States

In the United States (US), the use of psychedelics is governed by the Controlled Substances Act, classifying them as Schedule I drugs.[24] This classification indicates that there is a high risk of drug abuse and that the substance is not safe to use, even under medical supervision. Ketamine has been approved as a short-term anaesthetic and in 2019, the US Food and Drug Administration (FDA) approved esketamine, a chemical variation of ketamine, for the treatment of depression and suicidality.[25, 26] Ketamine clinics, spaces where ketamine can be prescribed as a treatment for depression, have emerged in the last few years.[27]

In 2017, supported by the evidence emerging from scientific research, the FDA designated two psychedelics, psilocybin and MDMA, as 'breakthrough' therapies.[23-15] A breakthrough therapy[26] designation allows the pharmaceutical company to speed up the development process while being offered additional regulatory guidance and support. The FDA can grant this designation to medications or therapies aiming to address serious medical conditions that offer significant advantages over existing treatments and the designation. For example:

- In 2017, the Multidisciplinary Association for Psychedelic Studies (MAPS), a US non-profit organisation, announced that the FDA had granted breakthrough therapy designation to MDMA for the treatment of PTSD[28]
- In 2018, COMPASS Pathways, a UK mental health care company, received a breakthrough therapy designation from the FDA, which enabled the company to carry out studies on psilocybin for treatment-resistant depression[29]
- In 2019, the FDA granted breakthrough therapy designation to the Usona Institute, a US medical research company, to further investigate the use of psilocybin in treatments for major depressive disorders[30]

In June 2023, the FDA published the first draft of guidance to highlight important considerations for industry stakeholders when designing clinical trials for psychedelic drugs.[31]

At the legislative level, an updated version of the Breakthrough Therapies Act was introduced to the US Congress in 2023. If the bill is passed, it will allow Schedule I drugs that have received breakthrough therapy designation by the FDA to be reclassified as Schedule II drugs, including psychedelics.[32]

Some of the US state legislations have already gone further. Oregon became the first US state to legalise adult use of psilocybin in January 2023, fuelled by high demands for improved mental health care.[33] A similar law is currently making its way through the Colorado State Legislature.[34] More broadly, there is a noticeable shift in the perception of psychedelics: 25 US states have already considered legislative bills that either propose to reform existing laws restricting access to psychedelic drugs or suggest further research into reforming legislation, and laws from seven states have been passed.[35] This trend is accelerating: the number of new psychedelic reform bills introduced each calendar year has increased from five in 2019 to 35 in the first eight months of 2022.[36]

Psychedelics research is largely undertaken (and financed) by private companies and non-profit organisations. The Schedule I classification of psychedelics means that federal funding for research is severely limited. Additionally, a provision inserted into US funding bills prohibits federal funding from supporting "any activity that promotes the legislation of any drug or other substance included in Schedule 1".[37]

M.4.2. The United Kingdom

In the UK, psychedelics are legislated under the Misuse of Drugs Act of 1971.[38] Controlled drugs are split into five groups depending on their potential level of harm, each subject to different control measures. LSD and psilocybin are categorised as a Schedule 1 drug and as such, require specific authorisation and licensing from the Home Office.[39] MDMA and ketamine are Schedule 2 drugs and therefore easier to access for research. Ketamine is licensed in the UK to be used by doctors as an anaesthetic. As a result, ketamine can also be prescribed 'off-licence' for depression and associated mental health challenges if it is deemed to have medical potential.[40]

Regulatory barriers to psychedelics research in the UK are beginning to change following significant scientific breakthroughs and investments.[25,26,27] The Medicines and Healthcare products Regulatory Agency (MHRA), which regulates medical treatments in the UK, introduced Innovation Passports in 2021 to accelerate time to market for promising medicines through a new regulatory pathway, the Innovative Licensing and Access Pathway (ILAP). In 2021 and 2022, the agency awarded Innovation Passports to three psychedelic-assisted therapies:

- MAPS for MDMA-assisted therapy for post-traumatic stress disorder (PTSD)[41]

- COMPASS Pathways for COMP360 psilocybin therapy for treatment-resistant depression[42]
- Small Pharma Ltd for SLO26, its formulation of the psychedelic DMT (N, N-Dimethyltryptamine), to treat patients suffering from major depressive disorder[43]

While this is not a change in the regulation of psychedelics per se, it signals that the MHRA is open to supporting psychedelic research and development.

The National Institute for Health and Care Research (NIHR) and the Medical Research Council (MRC) have provided funding for the development of psychedelic drugs, e.g. a £1.5 million commitment to the Awakn Phase III trial with ketamine-assisted therapy for the treatment of alcohol use disorders. The trial will be led by the University of Exeter and will be delivered at seven NHS sites across the UK.[44] The NIHR also provided funding for the Psilocybin in Depression Resistant to Standard Treatments (PsiDeR).[45]

Despite these public investments, experts suggested that research on psychedelic therapies is primarily funded by the private sector. For example, Clerkenwell Health, a clinical research organisation specialising in psychedelics, is touted as Europe's first commercial facility dedicated to psychedelic-assisted therapies. One example of an R&D company working at this hub includes OctarineBio, who are seeking to test synthetic psilocybin in clinical trials.[46] Clerkenwell has raised a total of £2.5 million in seed funding and aims to offer the infrastructure required to support psychedelics research.[47]

M.4.3. Germany

In Germany, psychedelics are governed under the controlled substances law, the Betäubungsmittelgesetz (Narcotics Law).[48] Under this law, psychedelics are illegal and considered unsuitable for therapeutic use. As in the UK, ketamine can be used for anaesthetic purposes and prescribed off-licence. As such, Germany offers ketamine-assisted therapy for patients with mental health conditions such as depression, anxiety, and post-traumatic stress disorder (PTSD).[49]

The German Federal Ministry of Education and Research (BMBF) provides funding for research on psychedelics. For example, in 2020, the BMBF awarded EUR 2.6m (£2.3m) in funding for a Phase III clinical trial testing the efficacy and safety of psilocybin in treatment-resistant major depression (EpIsoDE).[50] This study is the first psilocybin study conducted in Germany since the 1970s, and to date remains the only government-funded trial on psychedelics.[48] Exploring the philosophical, ethical, legal, and social questions related to the increase in interest in psychedelic therapies in Germany – the so-called 'psychedelic renaissance' - the Federal Ministry of Education and Research is funding the PsychedELSI project.[51] The project was awarded EUR 300k (£250k) and will run between 2023 and 2026, bringing together experts from anthropology, psychotherapy, philosophy, and law.

Germany is also home to one of the largest private companies operating in psychedelic medicine, atai Life Sciences.[52] In 2024, atai invested EUR 36 million ($40 million) in a company seeking to advance a formulation of DMT as a potential therapeutic for Treatment Resistant Depression (TRD).

In addition to government funding, the PsychedELSI project is currently examining philosophical, ethical, legal, and social questions around the so-called 'psychedelic renaissance' in Germany.[51] The project was awarded EUR 300,000 by the Federal Ministry of Education and Research and will run between 2023 and 2026. It brings together experts from anthropology, psychotherapy, philosophy, and law and hopes to better understand the resurgence of psychedelic therapies.

M.4.4. South Africa

In South Africa, the use of all psychedelic substances is criminalised under the Drugs and Drug Trafficking Act 140 of 1992 and the Medicines and Related Substances Act 101 of 1965.[53,54] However, the Director-General of the Department of Health may authorise the use of such substances for research purposes.[55] Ketamine, similar to other countries, is registered for anaesthetic purposes. The South African Society of Psychiatrists (SASOP) has recognised ketamine as therapy for treatment-resistant depression.[56]

An example of a South Africa-based study is a double-blind, randomised Phase II feasibility trial of psilocybin with supporting psychotherapy treatments, implemented by Canssun Medicinal, a private company.[57] Announced in 2023, the trial is investigating the use of psilocybin to treat HIV-positive women suffering from major depressive disorders.[55] Mental health conditions such as depression and anxiety pose an economic cost to South Africa; currently, more than US$12.5 billion is spent providing treatments and support to patients.[58] In sub-Saharan Africa in particular, an estimated 8.2 million people are living with HIV and major depressive disorder is a common co-morbidities.[59] As a result, biomedical companies are investing in new therapies and treatment modalities for South African patients, which also include psyschedelics.[57]

Currently, the South African government does not use public funds to support psychedelic research and as a result, research is only funded through private investments.

M.5. Research and Development Challenges

Despite promising results from several clinical trials, further research into the use of psychedelic compounds and their mechanisms of action is necessary to more fully understand their biological effects and to pave the way for their safe use in treating patients.[60] However, a range of scientific, regulatory, and societal challenges to psychedelics research and their clinical use persist, including:

- **Limited understanding of mechanism of action and biological effects**: Historically, robust *in vivo* and *in vitro* research has been required to bring pharmaceutical products to market.

However, due to regulatory barriers and associated financial barriers, only a relatively narrow range of the effects of psychedelic compounds and their mechanisms of action have been thoroughly investigated to date. Experts suggested that the use of *in silico* research, such as computational models and simulations in psychedelic research, is emerging as a viable solution to these regulatory barriers.[61] For example, recent *in silico* studies at the University of Toronto demonstrated insights into potential biomarkers, treatment targets, and the underlying mechanism of ketamine's therapeutic benefits to suicide prevention.[62] These findings can accelerate the progression to in-human studies. Recent advancements in Artificial Intelligence (AI) and Virtual Reality (VR) are expected to play an important role in modelling the effects of psychedelics.[61]

- **Methodological issues raising doubts about internal validity of studies**: Clinical studies involving psychedelics encounter several methodological issues.[63] Among these are a lack of control groups, often cited as a cost-saving measure, as there is insufficient funding to cover access the psychedelics and recruitment of a larger number of participants. Another key issue is the breaking blind problem, i.e. when participants guess that they have received the active drug, which is particularly challenging in psychedelic research and can lead to overestimations of the drug's effect. Attempts to address the breaking blind problem include assessing and reporting blinding efficacy, including an active control condition, recruiting participants without prior psychedelic experiences, and controlling for the breaking blind problem statistically.[64]
- **Increased patenting activity, potentially limiting innovation in the future**: As a result of recent promising clinical trial findings, many research organisations are now attempting to patent their 'new' psychedelic compounds. While psilocybin occurs naturally, patents have been granted for crystalline forms of the compound with an excipient, an inactive substance that serves as the medium for drug delivery. For example, in the UK, Compass Pathways has pursued patents on psilocybin compounds as well as the underlying methodology for the treatment of mental health conditions with psychedelics, which after challenges from activists have been granted.[65] However, these patents have attracted criticism from industry experts, scientists, journalists, and indigenous activists, who claim that the patents are unethical and exploit the traditional knowledge of indigenous groups who have historically used these compounds.[37] In addition, patents can limit access for other research organisations and stifle innovation in the field. This issue is not unique to psychedelic research, as patents in cancer therapies and other medical innovations have sparked similar debates.[66] To encourage

continued development of such therapies, experts suggested an approach similar to innovations under the COVID-19 pandemic, in which companies sign patent pledges promising not to enforce patents under certain conditions. Using the United States as an example, the Multidisciplinary Association for Psychedelic Studies and the Usona Institute both conduct clinical trials without patent rights.[37]

- **Regulatory barriers and associated high research costs:** Taking the UK as an example, experts highlighted that regulatory classification under Schedule 1 results in high costs for the import and storage of infrastructure. In a survey of medical professionals, the high cost of obtaining Schedule 1 drugs such as psychedelics for research in the UK was cited as a barrier to research. Specific facilities are required to store the compounds, including safes and cameras. In addition, funding was seen as a challenge as researchers cite a 'catch 22' situation in which they cannot apply for funding without securing the drug, and yet the drug cannot be secured without funding.[67] In the United States, Schedule I classification of psychedelics requires updated security protocols for laboratories, and it can take years to obtain full research approvals from the Drug Enforcement Agency (DEA) and an institutional review board.[67] In addition, the classification precludes research grants from federal sources (see above). As such, research on psychedelics is largely performed and funded by private organisations that have access to significant sources of funds.[68] In the absence of adequate public funding, private companies largely control the agenda of psychedelic research. Experts proposed that psychedelics could be rescheduled, which would enable more researchers, including from academic institutions, to study these compounds and increase research participation. [68,69,70]
- **Insufficient mental health infrastructure limiting patient recruitment and patient access**: Psychedelic studies also suffer from challenges that are endemic across the mental health sector. For psychedelic therapy studies that manage to progress to clinical trials, challenges remain due to insufficient infrastructure for mental health research. Experts highlighted that the majority of clinical trials fail due to recruitment issues and that this is felt particularly in the psychedelic research community.[69] Recruitment challenges occur for a variety of reasons, including barriers to participation, such as rigorous inclusion-exclusion criteria. Additionally, a significant portion of the population cannot access the healthcare system. Experts suggested addressing this challenge by working with patients at an early stage to minimise dropout. Taking the UK as an example, experts highlighted that the National Health Service (NHS) is working to streamline recruitment into clinical trials. Importantly,

experts also felt that drug developers are now much more aware of the importance of early feasibility trials than before, and how these can provide insights into improving the design of subsequent larger trials.

- **Persisting stigma and knowledge gaps of psychedelic-assisted therapy:** While the clinical benefits of psychedelics are becoming evident and their legal status is starting to change in some countries, widespread adoption will depend on healthcare providers' attitudes and ability to deliver psychedelic-assisted therapy. Persisting stigma and a lack of confidence in delivering psychedelic therapy could interfere with their use in medical settings.

  For example, two surveys of US-based psychologists and medical professionals conducted in 2018 and 2022 found that an overwhelming majority (81-85%) reported they believed psychedelic-assisted interventions deserved additional research.[70,71] At the same time, only around 45% of respondents felt that psychedelics "showed promise in treating psychiatric disorders". Additionally, a subset of the population (17-25%) reported that they believed psychedelics to be unsafe even under controlled medical supervision. A 2021 survey of UK psychiatrists suggested that stigma towards psychedelics may be lower amongst UK psychiatrists than among US psychiatrists, as 77.2% of respondents felt there was a role for controlled or therapeutic use of psychedelics.[72] However, around 64% of psychiatrists indicated that they were not at all prepared to deliver or participate in psychedelic therapy themselves. These findings suggest that additional training for medical professionals may be necessary to overcome current stigma and prepare the workforce to advise and deliver psychedelic therapies. Interestingly, the survey of UK psychiatrists indicated that psychiatrists in training felt better informed about psychedelic-assisted psychotherapy than non-training grade colleagues.

  Surveys of patients also suggest that there are broader concerns about safety, including adverse effects, illegality, and insufficient research.[73]

More broadly, experts suggested that governments and charitable organisations had an important role to play in finding solutions to both the developmental and regulatory challenges in the field of psychedelic therapeutics. Suggestions included bringing together community members to brainstorm solutions that work across multiple avenues of research, including professional bodies, research funders, and lived experience advocates.

Quote

A psychedeclis developer suggested that bringing the community together to find solutions to barriers might be a useful next step.

"Wellcome could fund one or more workshops with stakeholders to find solutions to these barriers. Participants may include:

- *Department of Health & Department of Business & Trade*
- *Home Office*
- *NICE*
- *Professional body associations for healthcare professionals*
- *MHRA*
- *Head of research funders e.g., MRC*
- *Pharma companies*
- *Key individuals such as Sally Davies (former Chief Medical Officer who recommended re-scheduling of cannabis-based drugs)"*

M.6. Lived experience perspectives

Advocacy groups and organisations play an important role in advancing research on psychedelics for therapeutic uses. One example is the Psychedelic Participant Advocacy Network (PsyPAN), which supports psychedelic research and development by creating a link between researchers/developers and people with lived experiences with psychedelics, whether they are already taking psychedelics or may be open to joining clinical trials. The UK-based non-profit organisation was founded in 2021 by Ian Roullier and Leonie Schneider, both of whom were participants in clinical trials using psilocybin to treat depression. PsyPAN's goal is to help improve the safety of individuals participating in psychedelic research and help create more effective treatments.74 Experts highlighted that the work carried out by the organisation provides researchers and developers with data on patients' experience of clinical trials which can improve the design of future research studies. PsyPAN's work in communicating the opportunities and challenges associated with psychedelics also contributes to broader efforts focused on the decriminalisation and the reduction of stigma surrounding these substances.[75]

In the US, a psychedelics coalition is growing its advocacy footprint. The Psychedelic Medicine Coalition, founded in 2021, has successfully campaigned to decriminalise psychedelic mushrooms in the District of Columbia (D.C.).[76] The group is now hiring lobbyists to seek to campaign for

the re-scheduling of psychedelics to enable wider therapeutic uses and clinical trials. [77]

In 2023, Australia became the first country in the world to legalise the use of psychedelics to treat some mental health conditions.[78] Approved psychiatrists can now prescribe MDMA to those suffering from PTSD and psilocybin for drug-resistant depression. Mind Medicine Australia (MMA) is a charity which lobbied for psychedelic treatments. MIND's work is informed by a lived experience panel with speakers who have suffered from mental health conditions and found relief through therapeutic psychedelics and those with family members who have suffered.[79] The charity is now training health professionals in procuring and prescribing treatments, and 'holding space' for patients undergoing psychedelic therapy, which is unlike the one- or two-hour therapeutic sessions that are normally delivered for patients. Lived experience is key to informing new practices. [78]

M.7. Conclusions

In the past decade, there has been a resurgence of interest and research into the therapeutic potential of psychedelics, driven by research, advocacy groups highlighting lived experience, and the pressing need for innovative treatments for substance dependence and mental health conditions. Psilocybin, MDMA, LSD and ketamine have shown promise in treating various conditions, ranging from addiction and depression to PTSD.

The regulatory landscape surrounding psychedelics across the globe is evolving. In most countries, the scheduling of psychedelics results in challenging regulatory barriers that prohibit increased research. A notable change in the international, regulatory landscape is Australia's recent legalisation of psychedelics to treat some mental health conditions. Elsewhere, breakthrough designations from the FDA in the United States, legislative changes in states like Oregon and Innovation Passports to psychedelic treatments in the UK demonstrate a shifting perspective on psychedelics.

Despite the promising results from recent clinical trials across the world, there remain developmental, regulatory, and societal challenges that threaten the future of psychedelic research. Legislation that regulates psychedelics as controlled substances inhibits further developments and has resulted in bloated administrative costs for groups or organisations that do undertake research. Taking the US as an example, funding guidelines enforced due to scheduling block the use of federal funding for psychedelic research and approval from regulatory bodies to study psychedelics can take years. And in the UK, the high cost and uncertainty around the procurement and subsequent storage of psychedelics increases the barrier to entry for research and development and prohibits many universities and other researchers from carrying out important work.

The resurgence of psychedelic research for mental health treatments is a complex and dynamic journey. The evolving regulatory landscape, coupled with existing challenges and emerging

opportunities, underscores the need for a collaborative, multidisciplinary effort to unlock the full therapeutic potential of psychedelics and mitigate the global burden of mental health disorders.

M.8. Sources

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Role	Organisation name	Date of interview
Head of Clinical Development	Atai Life Sciences	07/07/23
Professor of Neuropsychopharmacology, Director of the Neuropsychopharmacology Unit in the Division of Brain Sciences, Head of Centre for Psychedelic Research	Imperial College London, Centre for Psychedelic Research	24/08/23
Senior Clinical Trials Manager	Clerkenwell Health	21/11/23
Corporate Communications and Marketing Analyst	Clerkenwell Health	21/11/23

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Appendix N Mental Health Initiatives

N.1. Overview

Initiatives designed to improve mental health and wellbeing encompass a broad range of activities, many of which aim to address aspects of the mental health R&D ecosystem. These initiatives, typically driven by non-profit organisations, governments and/or other advocacy groups, can help to promote mental well-being, prevent mental health disorders, and improve access to mental health care. Common objectives and associated activities of mental health initiatives include:

- **Raising awareness** to encourage open discussions about mental health and reduce the stigma associated with mental health disorders. This, in turn, can have a positive effect on individuals' treatment-seeking behaviour or enrolment in clinical trials, for example.
- **Prevention and early intervention** in the form of educational programmes or community outreach activities can help individuals recognise and address mental health concerns before they escalate. Initiatives of this type have commonly been aimed at children and adolescents; and at adults by addressing well-being in the workplace.

  Advancing research and innovation in mental health is usually done through funding calls and grants to sponsor research programmes aiming to enhance the understanding of mental health conditions and their causes in order to improve treatment and implement research-based and innovative interventions. These initiatives are typically sponsored by non-governmental organisations (NGOs) and/or public bodies. More recently, however, venture capitalists, greatly driven by a growing market since the onset of the Covid-19 Pandemic, have been reportedly investing substantial amounts in mental health start-ups.[1] Venture Capitalists, such as *What If Ventures,*[2] *InHealth Ventures,*[3] or *Telosity Ventures*,[4] are actively investing in start-ups working on developing mental health digital services or interventions like apps and telehealth. Concretely, an analysis by *Sifted* reports that venture capitalists have invested £1.7 billion into mental health start-ups between 2020 and the end of 2022.[5] All in all, the research activities propelled by these types of initiatives are often carried out by a consortium of academic and non-academic actors, early career researchers or PhD candidates, and (small) private enterprises.
- **Training and capacity-building** initiatives for health professionals, practitioners, and social care workers, among others, can help to address a shortage of mental health professionals. Training programmes, guidance, or toolkits, for example, can aid professionals in diagnosing mental health disorders and prescribing the most efficient and appropriate intervention.

- **Improving access to affordable and quality mental health care services** such as therapy, psychiatric care, or counselling can have a positive impact on patients seeking and receiving the right kind of treatment for mental health disorders. Initiatives of this type are often, but not exclusively, aimed at LMICs where access to mental health services is scarce. These initiatives can also play a role in promoting the use of digital therapeutics and mobile applications for individuals with limited or difficult access to health facilities.
- **Advocacy for policy change** at a local (e.g., community or regional), national, or even global level can enact improved mental health legislation and policies. These can help to integrate mental health into the overall healthcare systems and/or persuade greater public spending to fund mental health research, for example.
- **Community support** programmes can help individuals and families cope with mental health challenges. These include helplines, forums, and educational material, among others.

These objectives are by no means mutually exclusive, and it is common for an initiative to address, at least indirectly, several of them. For instance, raising awareness of mental health conditions can help to advocate for policy change, which itself can have a positive effect on advancing research and innovation in mental health or in improving access to mental health services.

In the remainder of this section, we provide further information on approximately 30 mental health initiatives in the context of the priority barriers in the mental health R&D ecosystem. We first refer to a set of global initiatives being piloted by the World Health Organization (WHO) and the World Economic Forum (WEF); and then comment on a series of initiatives being driven by organisations in the United Kingdom, United States, and the European Union, as well as a small subset of initiatives taking place in Africa. We also comment, where applicable, on any results and (early) impacts of these initiatives, as well as the extent to which they have successfully reduced or mitigated issues concerning barriers to the R&D mental health ecosystem.

It is important to note that this list is not exhaustive. It is intended to provide an indicative snapshot of the current and bigger initiatives being implemented around the world concerning barriers to the mental health R&D ecosystem. As such, there may be other initiatives with a more general approach to addressing mental health and mental well-being that have not been included in this section.

N.2. World Health Organization (WHO)

The World Health Organization (WHO) recognises mental health as a fundamental component of overall health. The WHO works with Member States and partners to promote mental well-being, prevent mental disorders, and improve access to quality mental health care by providing countries with guidance and resources to enable

action. The Organization also plays an active role in supporting countries to integrate mental health into general healthcare systems, policy, and legislation; and in promoting innovative psychological interventions (e.g., digital devices), implementing prevention programmes aimed at children and adolescents, and improving access to quality and affordable mental health care in low- and middle-income countries (LMICs).

Notable initiatives driven by the WHO include the **Special Initiative for Mental Health (2019-2023): Universal Health Coverage for Mental Health**[6] aiming to provide "quality and affordable mental health care to an additional 100 million people in 12 priority countries." It is currently being implemented in nine countries, namely Argentina, Bangladesh, Ghana, Jordan, Nepal, Paraguay, Philippines, Ukraine, and Zimbabwe. The strategy and implementation plans concern developing or improving mental health policy and scaling up quality services in community-based and general health settings. In its initial phase, the participating countries have undertaken a landscape analysis to get a broad picture of mental health needs, available services, and opportunities and challenges to scale up mental health services.

Another initiative by the WHO is the ***Mental Health Gap Action Programme (mhGAP)***,[7] which has the objective of scaling up services for mental, neurological and substance use disorders. The mhGAP has produced an "Intervention Guide" to support non-specialist health workers around the world to build the capacity needed to deal with the growing burden of mental, neurological and substance use conditions, thus narrowing the treatment gap and improving intervention practices. Moreover, the **Helping Adolescents Thrive (HAT) Initiative**[8] is a joint WHO-UNICEF initiative to strengthen policies and programmes for the mental health of adolescents. The HAT Initiative has produced a "Guideline on promoting and preventive mental health interventions for adolescents" as well as a ToolKit for its implementation.

More broadly, the WHO's **Comprehensive Mental Health Action Plan**[9] sets out clear actions for Member States and other partners to achieve universal coverage for mental health services, while the **Global Health Observatory**[10] provides a means to disseminate information on mental health indicators to help countries strengthen their mental health systems and researchers to engage in mental health research.

It is difficult to assert with certainty the extent to which countries are adopting the practices and the extent to which the solutions proposed by these initiatives are being realised given their ambitious and widespread approach. Nevertheless, there have been some assessments of these initiatives, such as the Mid-Term Learnings Reports of the *Special Initiative* or country-specific impact assessments of the mhGAP, which suggest that there has been a substantial positive impact on training, patient care, research, and attitudes to mental health. All in all, there is an apparent indication that these initiatives have the potential to play an important role in addressing the

treatment gap and improving the affordability of mental health interventions. They are also taking an active role in promoting awareness of mental health conditions, thus addressing the stigma surrounding mental health disorders; and can address the shortage of mental health professionals through training, capacity-building activities, and tools such as intervention guides; as well as influencing policy and wider interventions.

N.3. World Economic Forum (WEF)

The World Economic Forum's (WEF) network of **Global Future Councils** provides a platform for knowledgeable thought leaders from academia, government, international organisations, business, and civil society to come together to "identify and disseminate transformative ideas with the potential for global impact."[11] Members are organised in expertise-based thematic Councils to provide strategic insights, scientific evidence, guidance, and a multidisciplinary understanding of major trending issues, spanning topics such as Artificial Intelligence and cybersecurity, to geopolitics and responsible investing.

The objective of the (Previous) **Global Future Council on Mental Health**[12] was to address the need for a properly funded and regulated global mental health ecosystem after the disruption to daily life brought about by the Covid-19 pandemic led to an extraordinary rise in rates of depression, anxiety, substance abuse, and other mental disorders, as well as a disruption to existing mental health infrastructures.

Recognising the potential role of new technologies, mental health apps and other digital services to address the mental health crisis, in April 2021 the Council published the **Global Governance Toolkit for Digital Mental Health: Building Trust in Disruptive Technology for Mental Health.**[13] The White Paper provides a policy framework to guide governments and regulators towards crafting successful policies on technology and mental health to help "improve the accessibility, quality and safety of services that support all members of society to meet their desired emotional, social, and psychological potential." Concretely, the aims of the toolkit are to helps its users to: (i) understand the potential for digital mental health; (ii) develop principles and standards for the safe and ethical implementation of digital mental health services; (iii) adapt, pilot and adopt these standards in health systems across the globe; (iv) improve the access, effectiveness, quality and safety of digital mental health solutions; (v) make strategic investment and incentivisation decisions in the digital mental health ecosystem to encourage growth; and (vi) make informed decisions to incorporate digital mental health tools into a health system seamlessly. It is worth noting that the toolkit was piloted by the New Zealand Ministry of Health while developing the Digital Mental Health and Addiction Services Evaluation Framework.[14]

N.4. United for Global Mental Health (UnitedGMH)

United for Global Mental Health (UnitedGMH)[15] is a global initiative

established in 2018. Its focus is on advocating for mental health to raise awareness, reduce stigma, and increase mental health care and support around the world. In line with its latest Strategy (2024-2026), the main work of UnitedGMH revolves around four strategic objectives:

1. Protecting mental health rights, i.e., advocating for rights-based and non-discriminatory mental health policies and legislation.
2. Improved mental healthcare systems, i.e., high quality, person-centred services and mental health support, as well as a well-resourced health workforce capable of delivering mental health services across healthcare systems.
3. Enabling ecosystems, i.e., increasing and improving finance for mental health in all policies, providing timely, representative, good-quality data on mental health, and promoting positive online environments for mental health and wellbeing.
4. Field building, i.e., improving coordination and capacity of the global mental health community, and amplifying the voices of people with lived experience.

Recent achievements highlighted by UnitedGMH include helping to secure additional financing and political support for child, youth and caregiver mental health; supporting the decriminalisation of suicide in Pakistan, Ghana, Malaysia, and Guyana; persuading *The Global Fund to Fight AIDS, Tuberculosis and Malaria* to incorporate mental health into its five-year strategy for the first time;[16] ensuring mental health features in new UN General Assembly resolutions; and expanding the mental health field through the growth of the Global Mental Health Action Network (GMHAN).[17]

N.5. United Kingdom

N.5.1. The National Institute for Health and Care Research (NIHR)

In the United Kingdom, the **National Institute for Health and Care Research (NIHR)**[18] funds research projects and supports training and career development for researchers in mental health, among other subjects. The NIHR also supports the delivery of this research on the NHS and in public health and social care settings. There are several mechanisms and numerous initiatives that the NIHR is leading to support this cause, including:

- **NIHR Funding Programmes.** A substantial form of support from the NIHR to advance research and innovation in mental health is through funding programmes. As of August 2021, the NIHR has supported 751 research studies in mental health investigating the diagnosing, prevention, and treatment of mental health conditions. For example,
  - In September 2023 the NIHR put out a call to establish up to ten **Mental Health Research Groups (MHRGs)**[19] in England to foster collaborations between higher education institutions to design and implement place-based solutions in areas with a high burden of mental health

conditions, limited local mental health research capacity, and low recruitment into mental health research studies.

- In August 2021 the NIHR and the Department of Health and Social Care (DHSC) announced a £30 million **Mental Health Research Initiative (MHRI)**[20] "in order to help tackle the disparity between regional needs and mental health research activity." Part of this funding is being used, for example, to finance the **Peninsula Mental Health Research Initiative (PenMHRI)**[21] launched to help tackle the gap between local need and mental health research activity.
- In November 2017, the NIHR issued a **themed call for research for the promotion of good mental health and the prevention or treatment of mental ill health**.[22] Issues of particular interest for this call included "proposals that utilise new digital health technologies or investigate their effects."

- **NIHR Clinical Research Network (CRN).**[23] The CRN (expected to transition to the **Research Delivery Network (RDN)** in April 2024) has been established to facilitate and support clinical research and health studies that require the recruitment of individuals. According to the NIHR, 70,767 participants were recruited across 327 studies in mental health research in 2019/20 and over 80% of non-commercial mental health studies have been delivered on time and to target.
- **NIHR Incubator for Mental Health Research.**[24] This was created to increase capacity in mental health research. The incubator, led by a steering group formed of NIHR mental health research professors and leaders from across NIHR infrastructure, will showcase mental health research and careers and share training opportunities for those interested in carrying out research in subjects related to mental health.
- **NIHR Mental Health Translational Research Collaboration (MH-TRC)**[25] and the **NIHR Biomedical Research Centres (BRC).**[26] Both consist of collaborations that bring together leading researchers in the field of mental health from across the UK to accelerate the translation of research findings and lab-based scientific breakthroughs into practical applications, such as new treatments, diagnostics, or medical technologies, in clinical settings. The MH-TRC is also expected to deliver NIHR's **Mental Health Mission (MHM)**[27,28] – a £42.7 million investment into mental research announced by the NIHR and the Office for Life Sciences in May 2023 – to develop innovative new interventions and technologies to diagnose, monitor, and treat mental ill-health. This funding is expected to be used to establish demonstrator sites, towards building mental health research capacity in the NHS and translating research findings into practice. Reportedly, the MHM will pay particular focus to "addressing barriers in research and supporting the development of

new industrial partnerships" and "enabling testing and trialling of interventions in location of significant need," thus providing a sustainable and research-ready environment that is able to support the needs to advance mental health research.

- **NIHR Policy Research Unit (PRU) in Mental Health**[29] conducts rapid research to inform the government making policy decisions about health and social care.

All in all, the NIHR itself is not an initiative but it is clear that NIHR funding programmes and other initiatives resulting from this are addressing a market failure for the purposes of advancing research in mental health. It is beyond the scope of this section to carry out a rigorous analysis of all specific mental health projects funded by the NIHR to provide a concrete indication of their impact.

N.5.2. UK Research and Innovation (UKRI)

One of UK Research and Innovation's (UKRI) "Areas of Investment and Support" is mental health. This is largely led by the Medical Research Council (MRC), which as of September 2023 is said to have invested more than £140 million over the last five years in "research directly addressing mental health questions."[30] Some examples of recent funding calls by UKRI and other UK research councils (such as MRC) include:

- **Adolescence, mental health and developing mind.**[31] This programme aims to fund research to investigate how mental health problems emerge in young people and methods of early intervention to promote positive mental health and well-being. The call amounts to £35 million and is expected to run between 2019 and 2026.
- **Mental Health Platform Hubs.**[32] This initiative is expected to start in April 2024, and amounts to a total of £17.5 million (£2-£3.5 million per award). This initiative aims to establish multidisciplinary and interdisciplinary hubs to carry out impactful research at scale on key areas of strategic needs in mental health.
- **Mental Health Research Networks.**[33] Eight mental health networks have been set up by UKRI to bring researchers, charities, and other organisations together to address important mental health research questions. The exact nature of these networks is varied, but mostly concerns raising awareness of mental health and promoting mental well-being.

N.5.3. MQ Mental Health Research

MQ is a non-profit organisation/charity that funds research in mental health. Their overall Transforming **Mental Health Initiative**[34] aims to further our understanding of mental health, improve treatments, and prevent mental illness. The organisation has a strict approach to research, specified as data-driven, inclusive, sustainable, and collaborative. To date, MQ has funnelled £23 million into its different research programmes including the "**Fellows Award**" programme aimed at early career scientists, and the "**PsyImpact**" programme that works to

get more people to get the right treatment, among others.

N.5.4. The Wolfson Foundation Mental Health Initiative

As part of its **Mental Health Initiative**,[35] in 2019 the Wolfson Foundation awarded £10 million to create the Wolfson Centre for Young People's Mental Health in Wales. The initiative aims to research how and why adolescent depression develops, as well as investigate the best methods for prevention and treatment.

N.5.5. Psychiatry Consortium

The **Psychiatry Consortium**,[36] launched in 2019, is a collaborative platform between two medical research charities and eight pharmaceutical companies aiming to drive innovation in psychiatric drug discovery. The main objectives of the initiative are to provide funding and support services for mental health research that brings together and involves individuals across all aspects of the research landscape (i.e., people with lived experience of mental health, academics, researchers, regulators, and industry scientists). To this end, the Consortium has committed £4 million in research funding to deliver up to 10-high-value early-phase drug discovery projects. The funding scheme, available to universities, research institutes, and small companies worldwide, provides successful applicants with access to drug discovery expertise and support for project management, delivery, and development.

The Psychiatry Consortium is managed by the **Medicines Discovery Catapult** and supported by **Wellcome**. So far, the Consortium reports to have engaged with over 400 research institutions in 75 countries worldwide, presented at international conferences, and delivered workshops and webinars to bring together key players in the mental health research landscape. Its current portfolio includes three projects investigating the KALRN, NEGR1, and GALR3 genes as novel targets for the treatment of schizophrenia, depression, and post-partum depression, respectively.[37]

N.5.6. The National Institute for Health and Care Excellence (NICE)

The **National Institute for Health and Care Excellence (NICE)** is a public body in the United Kingdom that operates as an independent organisation providing evidence-based guidance and advice to improve health and social care. There is guidance available for numerous conditions and diseases including mental health, behavioural and neurodevelopmental conditions. The guidance is in the form of guidelines for the identification and management of mental health disorders (including anxiety and depression), intervention and procedures guidelines, and health technology assessments (HTA).

NICE is active in developing **early value assessments (EVAs)** of MedTech[38] that allow "rapid assessment of digital products, devices and diagnostics for clinical effectiveness and value for money" as part of its health technology assessments. NICE has published EVAs on digitally enabled therapies for adults with anxiety[39] and depression,[40]

virtual reality technologies for treating forms of psychosis,[41] and self-help digital cognitive behavioural therapy for children and young people with symptoms of anxiety,[42] among others.

N.5.7. The Medicines and Healthcare products Regulatory Agency (MHRA)

The **Medicines and Healthcare products Regulatory Agency (MHRA)**[43] acts as the regulatory body responsible for ensuring the safety, quality, and efficacy of medicines and medical devices in the United Kingdom. In October 2022, the MHRA (in partnership with NICE) was awarded £1.8m of funding by **Wellcome** to explore and produce guidance on regulating digital mental health tools.[44] The work of the MHRA and NICE is expected to improve regulatory certainty and safety in digital mental health products by reviewing key aspects of medical device regulations and engaging with people with lived experience, experts, and international partners. The expected results of this project are said to include "published guidance documents to make clear the regulation and evaluation of these technologies for patients, the public, healthcare professionals and developers."[45]

N.6. United States

N.6.1. National Institute of Mental Health (NIMH)

The **National Institute of Mental Health (NIMH)**[46] is one of the 27 Institutes and Centres that make up the National Institute of Health (NIH) in the United States. The NIMH is committed to transforming the understanding and treatment of mental health and illnesses by supporting and conducting fundamental and clinical research, supporting the training of scientists to carry out basic and clinical mental health research, and communicating with all stakeholders about mental health research advances and priorities.

The NIMH also acts as a gateway to mental health information such as statistics on the prevalence and treatment of mental illness in the United States, and information for individuals considering taking part in clinical trials. The NIMH also supports research at universities and medical centres via grants and other cooperative agreements to carry out clinical research and training. Its current "Priority Research Areas" are listed as: Suicide Research, Genomics Research, Mental Health Disparities Research, and Global Mental Health.

A relevant example of an initiative supported by the NIMH is the **Fast-Fail Trials (FAST)**[47] initiative that ran between 2012 and 2015. The initiative was focused on enhancing the early phases of drug development by providing a rapid way to clinically test new or repurposed compounds for their potential use as psychiatric medications. Among others, FAST showed that a resting measure of brain activity could be used to measure medication effects in the brain; identified reward and pleasure receptors as a promising target for drug development in future clinical trials of treatments for mood and anxiety disorders; and showed that a brain imaging-based biomarker could

be used to develop glutamate-targeting medications to treat schizophrenia. Some other examples of initiatives arising from NIMH funding are described further down in this section (e.g. the One Mind AURORA Initiative).

N.6.2. One Mind

One Mind is a non-profit organisation dedicated to advancing research, awareness, and support for individuals affected by brain-related disorders and mental health challenges. The organisation focuses on fostering collaboration among researchers, healthcare professionals, policymakers, and other stakeholders to accelerate scientific discoveries and improve the diagnosis and treatment of brain disorders. The organisation is committed to transforming the world's mental health through: (i) science, i.e. advancing understanding, diagnosis, and treatment of mental health illnesses through research; (ii) business, i.e. through scale implementation of mental solutions and through entrepreneurship; (iii) media, i.e. content to promote positive attitudes towards mental health.[48] Some examples of One Mind's initiatives include the following:

- **One Mind Accelerator.**[49] This initiative supports early-stage start-ups with networking, education, and capital to rapidly build category-defining companies that improve the lives of people living with mental illness. Some of the listed key focus areas include biomarkers & diagnostics, and digital therapeutics.
- **One Mind AURORA.**[50] This is a national research initiative that works to improve the understanding, resilience, and recovery of individuals who have experienced a traumatic event. This initiative is supported by the NIMH and led by scientists at various universities in the US. The initiative proposes an extensive longitudinal and data-driven study to deliver the tools in physiology, genomics, neuroimaging, and wearable technology for clinicians to make informed decisions about trauma survivors' risk and care.
- **One Mind PsyberGuide.**[51] This initiative was established in 2013 as a direct response to the need for guidelines for individuals to navigate the health app marketplace. The initiative provides a gateway to unbiased expert reviews of mental health apps and digital health resources.

N.6.3. Clinical Trial Transformation Initiative (CTTI)

This initiative more broadly addresses issues related to clinical trials, such as high failure rates or long timeliness and delays. The **Clinical Trials Transformation Initiative (CTTI),**[52] co-funded by the U.S. Food and Drug Administration (FDA) and Duke University in 2007, brings together all stakeholders (i.e. patients, clinicians, ethics board representatives, sponsors, payors, healthcare systems leaders, and regulators) to discuss, exchange ideas, and work together on evidence-based solutions. This initiative provides a pathway towards designing trials with a quality approach, building digital health trials, using novel clinical trial designs,

enhancing patient engagement, supporting investigators & sites, and ensuring ethics & human research protections.

N.6.4. Foundation for the National Institutes of Health (FNIH)

The **Foundation for the National Institutes of Health (FNIH)**[53] is a non-profit organisation that supports the mission of the NIH in the United States. The main goal of the FNIH is to facilitate public-private partnerships to advance biomedical research and the development of new medical treatments and technologies. The organisation serves as a platform for collaboration and fundraising to enable innovative research initiatives and projects to thrive.

One of the initiatives managed by the FNIH is the **Accelerating Medicines Partnership (AMP)**.[54] The AMP is a multi-stakeholder, international public-private partnership between the NIH and the FDA in the United States, the European Medicines Agency (EMA), pharmaceutical and life sciences companies, and other non-profit organisations. One of the projects of the AMP is the **AMP Schizophrenia (SCZ)**[55,56] programme launched in 2020 to develop tools that can help to identify early stages of risk for schizophrenia, predict the likelihood of progression to psychosis, and identify new targets for drug-based treatments that can be tested in clinical trials. Formally, the goals of the AMP SCZ are to:

1. Validate biomarkers needed to identify clinical high-risk (CHR) individuals, predict the likelihood of progression to psychosis and other outcomes, and pinpoint metrics that can be used to assess early signs of treatment efficacy.
2. Establish a research network with U.S. and international sites focused on CHR populations, making research results more applicable to clinical trials globally.
3. Enable the identification of CHR individuals for inclusion in clinical trials.
4. Create a research framework that lays a foundation for future development of faster, more robust interventions.
5. Disseminate research data to the broader scientific community through the NIMH Data Archive platform, allowing faster translation of findings into solutions.

To this end, private-sector partners will reportedly invest a combined total of USD 18.3 million over five years through the FNIH, and the NIMH will contribute USD 99.4 million. The FDA and EMA is expected to provide regulatory guidance on biological markers of disease progression, outcome measures and endpoints for clinical trials.

As of February 2024, the NIMH is currently supporting three research projects as part of the AMP SCZ initiative. Specifically, the **Trajectories and Predictors in the Clinical High Risk (CHR) for Psychosis Population: Prediction Scientific Global Consortium (PRESCIENT)** and the **ProNET: Psychosis-Risk Outcomes Network** projects aim to facilitate selection of CHR individuals to enrol in clinical trials and monitor

disease progression and outcomes through the collection and mapping of biomarkers; and the **Psychosis Risk Evaluation, Data Integration, and Computational Technologies (PREDICT)** project will create a data processing, analysis, and coordination centre using the data generated by the other projects to develop algorithms that can identify biomarkers predictive of CHR outcomes.

Among other initiatives, the FNIH also manages **The Deeda Blair Research Initiative For Disorders of the Brain.**[57] The mission of this initiative is to accelerate basic research to discover new targets and approaches for therapy to improve the diagnosis and treatment of severe mental illness, including anxiety, depression, bipolar disorder, and psychotic disorders. As of 2023, there are seven individuals that have been awarded grants as part of initiative for proposals ranging from developing tools to help psychiatrists integrate neuroscience into clinical practice to identifying the molecular mechanisms of metabolic reprogramming in psychiatric illnesses, among others.

Lastly, and also managed by the FNIH, the **Biomarkers Consortium (BC)**[58] has the stated mission to "create and lead cross-sector efforts that validate and qualify biomarkers and other drug development tools to accelerate better decision-making for the development of new therapeutics and health technologies." The accomplishments of the BC to date, however, do not currently refer to advancements in this area for mental health disorders, but may pave the groundwork for future developments (e.g., the AMP SCZ programme).[59]

N.7. European Union (incl. Germany)

N.7.1. European Commission

As a result of the worsened mental health situation in the European Union, the European Commission's **Comprehensive Approach to Mental Health**[60] initiative was announced in June 2023. The initiative has introduced 20 flagship initiatives with €1.23 billion in funding from different instruments. This approach is wide in scope and efforts cover eight broad areas. In the list below we refer to the areas and corresponding initiatives that we find to be most relevant to addressing the priority barriers in the mental health R&D ecosystem:[61]

- Promoting good mental health, prevention and early intervention for mental health problems, which include the **European Depression and Suicide Prevention Initiative**, the **Access gate for people experiencing mental health issues Initiative**, and the development of the **European Code for Mental Health**.
- Reinforcing mental health systems and improving access to treatment and care, including the Initiative for more and better-trained professionals in the EU and the Initiative for Gathering data on mental health.
- Breaking through stigma, including the Tackling stigma and discrimination Initiative.

Additionally, the are numerous (both past and present) funding and tender opportunities sponsored by the European Commission aimed at advancing mental health research, interventions, and policy, many of which are part of wider funding programmes. For instance, arising from the **Horizon 2020**[62] (2014-2020) research and innovation funding programme, the **IMMERSE**[63] project (2021-2025, approx. €4m) is working towards creating a clinical digital mental health tool that uses mobile sensing data and innovative machine learning models using Experience Sampling Methodology (ESM) to treat mental health disorders; the objective of the **ERC APPLAUSE**[64] project (2017-2019, approx. €150th) was to develop a mobile app that facilitates access to mental health services and treatment for young people with mental health problems; the objectives of the **Mind Gap**[65] project (2018-2019, approx. €71th) was to trial and implement *Internet-assisted treatments based on Cognitive Behavioural Therapy (ICBTs)* for anxiety and depression to improve access to mental health services; and the **NEVERMIND**[66] project (2016-2020, approx. €5m) devised an e-health system consisting of a wearable smart sensing monitoring device (i.e., a "smart shirt") connected to a mobile application with lifestyle behavioural advice to recognise and be able to reduce depressive symptoms among patients diagnosed with severe somatic conditions.

As the successor to Horizon 2020, the **Horizon Europe**[67] (2021-2027) funding programme for research and innovation is also funding projects revolving around mental health research. For example, the **PsyPal**[68] project (2024-2027, approx. €6.5m) will examine the clinical effect of individualised and patient-centred Psilocybin Therapy, which itself can have the potential to encourage wider legislative changes towards decriminalising psychedelics for medical research and encourage more innovation into alternative treatment options for mental health disorders; and the **ENGAGE**[69] project (2023-2028, €1.5m) aims to improve digital mental health interventions by collecting information into how users engage and disengage with digital mental health interventions.

N.7.2. Accelerating Clinical Trials in the EU (ACT-EU) Initiative

The European Commission (EC), the Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMA) launched the **Accelerating Clinical Trial in the EU (ACT-EU)**[70] initiative to transform how clinical trials are initiated, designed and run. The aim of the initiative is to further develop the EU as a competitive centre for innovative clinical research and to further promote the development of high quality, safe and effective medicines requiring clinical trials. The initiative was launched in January 2022. Some of the activities and deliverables listed under its 2023 workplan include: supporting academic sponsors in enabling large multinational clinical trials; supporting sponsors to make use of available Clinical Trial Regulation (CTR) and Clinical Trials Information Systems (CTIS) training activities; setting up a

multi-stakeholder platform; supporting the adoption and implementation of revised EU guidelines in clinical trial design; and developing guidance on decentralised clinical trials.

N.7.3. The European Alliance Against Depression (EEAD)

The EEAD[71] is a community-based multi-level intervention program comprising of training for General Practitioners, public awareness campaigns, training of community facilitators, and support for patients and their relatives. There are some studies evaluating the impact of the programme that have found that it has had a positive effect in reducing suicide rates in some regions in Germany (German Alliance Against Depression[72]), Portugal and Hungary that had implemented the full programme, but there are other regions in these countries where the programme did not have any significant effects in reducing suicide rates.[73]

N.7.4. German Federal Ministry of Education and Research (BMBF)

The Federal Ministry of Education and Research (BMBF) in Germany is responsible for funding several mental health initiatives. For example, the **German Centre for Mental Health**[74] brings together high-level German universities, research institutions and hospitals working on aspects of mental health to encourage interdisciplinary collaborations, with a key focus on enhancing the appeal of mental health research careers through the "Clinical and Medical Scientists Programmes". The overall objective of the Centre is to improve the diagnosis, treatment and prevention of mental illnesses. This initiative considers factors such as gender equality, the alignment of career paths with family life, and the attraction of skilled academics from around the world.[75] Also funded by the BMBF, the **Centre for Intervention and Research on Adaptive and Maladaptive Brain Circuits (C-I-R-C)**[76] is a collaborative initiative by researchers in the German cities of Jena, Halle, and Magdeburg. It aims to provide a "transdisciplinary platform of application-oriented neuroscience to investigate specific neural and immune access points that shape adaptive and maladaptive brain circuits underlying behaviour in mental disorders in patients of all age groups."

N.7.5. Innovative Health Initiative (IHI) and Innovative Medicines Initiative (IMI)

The **Innovative Health Initiative (IHI)**[77] is the successor of the **Innovative Medicines Initiative (IMI)**.[78] The IHI is an EU public-private partnership funding health research and innovation. The core objective of the IHI is to "translate health research and innovation into tangible benefits for patients and society" by funding projects that address public health needs, improve patients' lives, and boost the competitiveness of Europe's health industries globally. The IHI has a reported budget of €2.4 billion for the period 2021-2027,[79] and awards funding through periodic thematic calls. As of January 2024, seven IHI calls have been launched since June 2022. One of the topics for IHI call 3 explicitly called for proposals to investigate digital health technologies for the prevention and personalised

management of mental disorders and their long-term health consequences.

The IMI operated in a similar style to the IHI. A total of 34 funding calls, spread across two programmes (IMI1 and IMI2), were made between April 2008 and June 2020.[80] Some of the projects concerning mental health that resulted from the IMI calls include:

- **NEWMEDS**[81] (2009-2015) set out to find novel methods for treating depression and schizophrenia. The project developed standardised and more accurate animal models and biomarkers to facilitate targeted clinical trials and personalised treatments.
- **PRISM**[82] (2016-2019) carried out a range of tests on patients with neuropsychiatric disorders to determine which biological parameters can be matched with specific clinical symptoms to bridge the translation gap between discovery and validation of biomarkers.
- **RADAR-CNS**[83] (2016-2022), i.e. Remote Assessment of Disease and Relapse in Central Nervous Systems Disorder, aimed to develop new ways of monitoring depressive disorders using wearable devices and smartphone technology, and thus be able to predict when relapses will happen and improve the treatments to stop them from occurring.

N.8. Africa (incl. South Africa)

N.8.1. African Mental Health Research Initiative (AMARI)

The **African Mental Health Research Initiative (AMARI)**[84] is mainly focused on capacity building to develop mental, neurological and substance use research in Ethiopia, Malawi, South Africa, and Zimbabwe. The main target groups of the initiative are fellows across MPhil, PhD and post-doctorate programmes that can engage in intense training programmes to secure future. The initiative is part of the Wellcome Trust's programme for Developing Excellence in Leadership, Training and Science (DELTAS) in Africa.

N.8.2. Centre for Mental Health Research and Initiative (CEMHRI)

The **Centre for Mental Health Research and Initiative (CEMHRI)**[85] is a non-profit organisation dedicated to promoting mental health awareness and eliminating the stigma associated with mental illnesses in Nigeria. The vision of the centre is to become a leading centre of excellence in Africa that provides information, research, data, and services in mental and neurological health. Some of the specific objectives of the CEMHRI include organising seminars and workshops to create awareness, disseminate information and build the capacity of health workers and general population in preventing, managing, and coping with mental illness.

N.8.3. South African Federation for Mental Health (SAFMH)

The **South African Federation for Mental Health (SAFMH)**[86] is a non-

profit organisation dedicated to promoting mental health and well-being in South Africa. The focus of the SAFMH is on advocating for the rights of individuals with psychosocial disabilities and plays an active role in raising awareness, reducing stigma, and supporting policies that enhance mental health services and inclusion.

N.8.4. South African Medical Research Council (SAMRC)

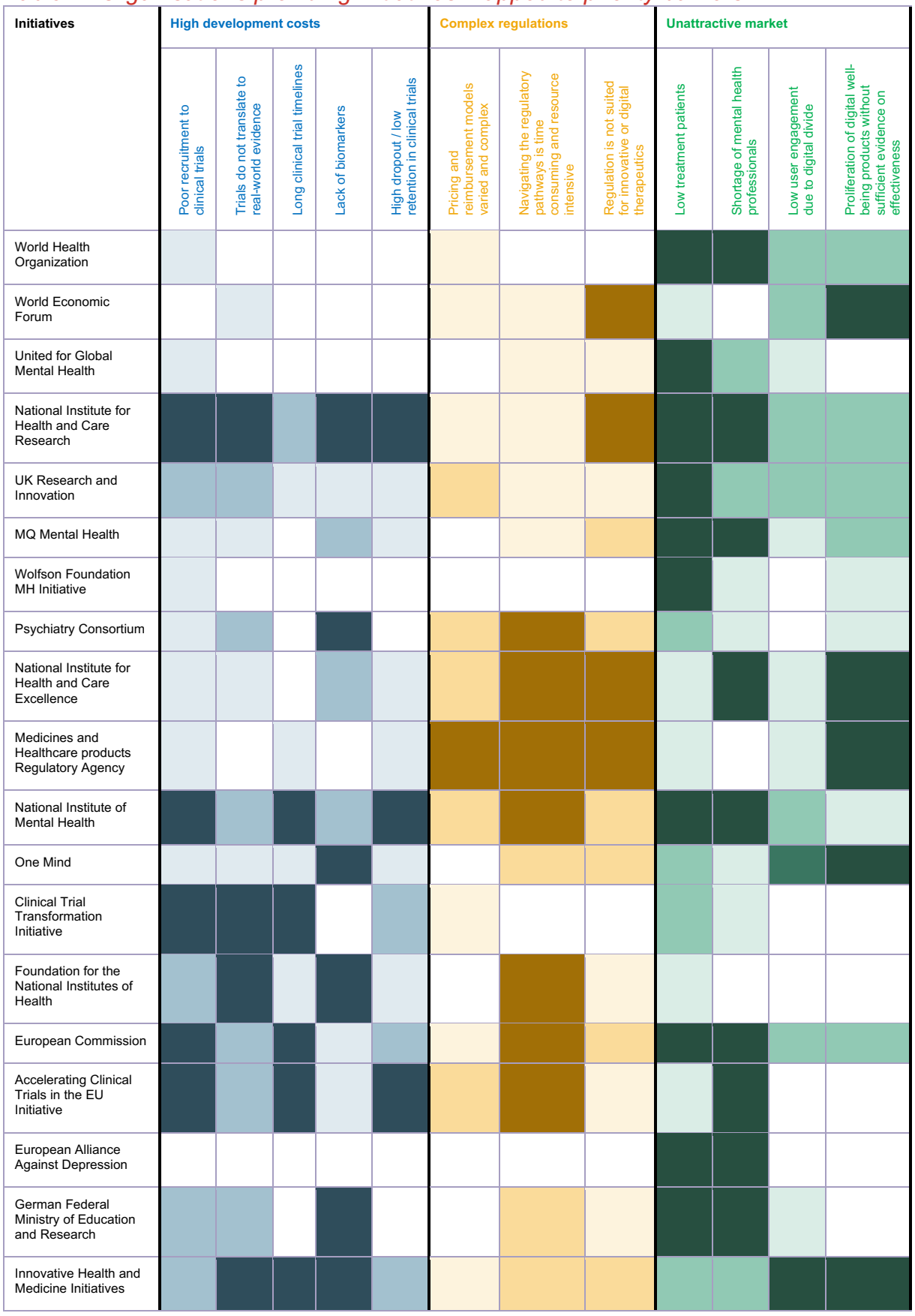
The **South African Medical Research Council (SAMRC)**[xxxi] is South Africa's largest funder of health research, medical diagnostics, medical devices, and therapeutics. Its mission is "to advance the nation's health and quality of life and address inequity by conducting and funding relevant and responsive health research, capacity development, innovation and research translation." The SAMRC's **Mental Health, Alcohol, Substance Use and Tobacco Research Unit (MASTRU)**[xxxii] conducts high-quality scientific research to inform policy, healthcare services, and interventions which promote mental health in South Africa. Some of the Unit's key focus areas include collecting accurate epidemiological data about the prevalence, causes and consequences of mental health problems; designing and evaluating interventions to promote mental health; and facilitating the implementation of scientific advances and evidence-based interventions through knowledge translation, advocacy work and providing information to policymakers and service providers. One of its current projects known as **Project MIND**[xxxiii] involves developing interventions for depression for patients receiving chronic disease care.

[xxxi] https://www.samrc.ac.za/about-us/who-we-are

[xxxii] https://www.samrc.ac.za/research/intramural-research-units/MASTRU

[xxxiii] https://projectmind.mrc.ac.za/index.html

Table A Organisations providing initiatives mapped to priority barriers



Initiatives	High development costs					Complex regulations			Unattractive market			
	Poor recruitment to clinical trials	Trials do not translate to real-world evidence	Long clinical trial timelines	Lack of biomarkers	High dropout / low retention in clinical trials	Pricing and reimbursement models varied and complex	Navigating the regulatory pathways is time consuming and resource intensive	Regulation is not suited for innovative or digital therapeutics	Low treatment patients	Shortage of mental health professionals	Low user engagement due to digital divide	Proliferation of digital well-being products without sufficient evidence on effectiveness
African Mental Health Research Initiative												
Centre for MH Research and Initiative												
South African Federation for Mental Health												
South African Medical Research Council												

Key: Darker shading indicates that the initiative addresses the priority barrier directly.

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