**Study Title:**  Cognitive and behavioural biomarkers for the treatment of mental health conditions: an investigation of acceptability and efficacy when used as a therapeutic tool

**Short title:** Cognitive and behavioural biomarkers in mental health therapy

**IRAS Project ID:** 281261

**Date and Version No:** Version 1 – 6th March 2020

|  |  |
| --- | --- |
| **Chief Investigator:** | Dr Ana Catarino, Ieso Digital Health, The Jeffreys Building, Cowley Road, Cambridge CB4 0DS.  T: **0800 074 5560**  E: [a.catarino@iesohealth.com](mailto:a.catarino@iesohealth.com) |
| **Investigators:** | Mrs Sarah Bateup, Ieso Digital Health  Dr Andy Blackwell, Ieso Digital Health  Dr Ana Catarino, Ieso Digital Health  Dr Ronan Cummins, Ieso Digital Health  Dr Michael Ewbank, Ieso Digital Health  Dr Valentin Tablan, Ieso Digital Health |
| **Sponsor:** | Ieso Digital Health  Contact: Annie Owen  Ieso Digital Health  The Jeffreys Building  Cowley Road  Cambridge  CB4 0DS  T: 0800 074 5560  E: [a.owen@iesohealth.com] |
| **Co-sponsor** | Biotaware Ltd  Contact: Simon Morris  Biotaware Ltd  2 Broadway  Lace Market  Nottingham  NG1 1PS  T: 020 8817 5249  E: [simon.morris@biotaware.com] |
| **Funder:** | Innovate UK |
| **Chief Investigator Signature:** |  |

**Table of Contents**

[Summary 3](#_Toc33801220)

[Synopsis 4](#_Toc33801221)

[Background and rationale 5](#_Toc33801222)

[Objectives 6](#_Toc33801223)

[Study design 7](#_Toc33801224)

[Clinical outcomes 9](#_Toc33801225)

[Patient identification 9](#_Toc33801226)

[Inclusion criteria 10](#_Toc33801227)

[Exclusion criteria 10](#_Toc33801228)

[Therapist training 10](#_Toc33801229)

[Study procedures 10](#_Toc33801230)

[Informed consent 10](#_Toc33801231)

[Early discontinuation and withdrawal 12](#_Toc33801232)

[Payment 13](#_Toc33801233)

[Statistics and data analysis 13](#_Toc33801234)

[Sample size 13](#_Toc33801235)

[Analyses 13](#_Toc33801236)

[Data management 14](#_Toc33801237)

[Risk assessment 15](#_Toc33801238)

[Study monitoring 17](#_Toc33801239)

[References 18](#_Toc33801240)

# Summary

Mental health disorders constitute an enormous healthcare concern, with one in four people estimated to be affected. Mental health problems are one of the main causes of the overall disease burden worldwide, causing 40 million years of disability in 20 to 29 year olds (Lozano *et al.*, 2012; Vos *et al.*, 2016). In the UK alone, the global economic cost of mental illness is estimated at £105bn per annum. However, despite the high prevalence of these disorders and the huge human, societal and economic cost, global median government mental health expenditure per capita represents less than 2% of total health expenditure. Not surprisingly, access to care remains poor across the globe, and clinical outcomes have remained stagnant for decades (World Health Organization, 2011; World Health Organisation, 2014).

The current study aims to collect and explore the potential value of digital cognitive and behavioural biomarkers in augmenting the therapeutic benefits of cognitive behavioural therapy (CBT), delivered by a qualified clinician. Examples of these cognitive and behavioural biomarkers include feature of patient language, summary measures of patients’ physical activity, geolocation, and patterns of social media use and digital interaction.

The central vision for this project is to explore this currently uncaptured contextual information that could be vitally important to both the patient and the CBT therapist. The aim of the project is to use this contextual information to create digital mental health monitoring tools, to be used by the patient and the therapist, to develop personalized treatment protocols that optimize clinical outcomes.

The enclosed project is defined by the following objectives:

* **Define a range of cognitive and behavioural biomarkers** and explore the relationships between these biomarkers and symptoms of common mental health disorders such as anxiety and depression;
* **Assess the acceptability of collection of cognitive and behavioural biomarkers** and the degree to which patients are willing to volunteer this information within a therapeutic context;
* **Develop digital mental health monitoring tools**, to be used by both patients and therapists, that provide the users with visibility on important cognitive and behavioural biomarkers that have shown to be correlated with mental illness;
* **Evaluate the effectiveness of digital mental health monitoring tools** in providing additional patient information to the therapists, which allows them to personalize treatment protocols with the aim of optimizing clinical outcomes.

The innovation in this project is defined by:

* Using artificial intelligence and natural language processing to define cognitive and behavioural biomarkers, and exploring their relationships with markers of mental illness;
* Evidence-based development of digital mental health monitoring tools, informed by correlations between cognitive and behavioural biomarkers and improvement or deterioration in mental health symptoms;
* The evaluation of the efficacy of digital mental health monitoring tools, when used by therapists to inform personalization of care, with the aim of improving clinical outcomes for patients.

# Synopsis

|  |  |  |  |
| --- | --- | --- | --- |
| **Study Title** | Cognitive and behavioural biomarkers for the treatment of mental health conditions: an investigation of acceptability and efficacy when used as a therapeutic tool | | |
| **IRAS ref no. / Short title** | Cognitive and behavioural biomarkers in mental health therapy | | |
| **Sponsor** | Ieso Digital Heath  The Jeffreys Building  Cowley Road  Cambridge  CB4 0DS  T: 0800 074 5560  E: [thelab@iesohealth.com](mailto:thelab@iesohealth.com) | **Co-Sponsor** | Biotaware Ltd  2 Broadway  Lace Market  Nottingham  NG1 1PS  T: 020 8817 5249  E: [simon.morris@biotaware.com](mailto:simon.morris@biotaware.com) |
| **Funder** | Ieso Digital Health | | |
| **Study Design** | Randomised controlled trial of patients receiving Internet-enabled CBT (IECBT) for the treatment of a mental health disorder, delivered by a qualified Psychological Wellbeing Practitioner (PWP) or a high intensity CBT therapist. Consenting patients will be randomised at start of treatment to one of two groups:   1. Therapist and patient visibility: Patients in this group will be given a fitbit and access to a mobile app that allows them to track their activity, location, social interaction and digital interaction biomarkers against their mood. Therapists delivering therapy will also have access to these biomarkers and use this information to tailor the care delivered to each patient and monitor patient outcomes. 2. Patient visibility only: patients in this group will be given a fitbit and access to a mobile app that allows them to track their activity, location, social interaction and digital interaction biomarkers against their mood. Therapists will not have access to patients’ biomarker data. | | |
| **Study Participants** | Patients referred to Ieso Digital Health, receiving Internet-enabled CBT for the treatment of a mental health disorder. | | |
| **Sample Size** | 200 patients in total. 100 patients allocated to the Biomarker enhanced therapy – therapist and patient group, 100 patients allocated to the Biomarker enhanced therapy – patient only group. | | |
| **Planned Study Period** | Total project length = 8 months. | | |
| **Planned Recruitment period** | July 2020 – March 2021. | | |
| **Primary objectives** | The primary research objective is to explore the efficacy of digital mental health monitoring tools in providing additional layers of patient information to the therapist, allowing them to personalize care with the aim of improving clinical outcomes. | | |
| **Secondary objectives** | The secondary research objective is to assess the acceptability of these digital mental health monitoring tools, and assess the degree to which patients are willing to volunteer this information within a therapeutic context. | | |

# Background and rationale

Mental health disorders, such as depression and anxiety disorders, are prevalent, costly, and in need of timely treatment interventions. In the UK alone, the global economic cost of mental illness is estimated at £105bn per annum. Despite the high prevalence of these disorders, and the economic, human and societal costs, access to care remains poor across the globe, and clinical outcomes have remained stagnant for decades (World Health Organization, 2011; World Health Organisation, 2014).

In the short and medium term, effective treatments for mental health disorders are available, including psychological therapies such as CBT, self-help approaches based on CBT principles, and pharmacological treatments (Hunot *et al.*, 2007; National Institute for Health and Clinical Excellence, 2011). While there is evidence that pharmacological approaches combined with psychotherapy comprise one of the most effective treatments to date (Khan *et al.*, 2012), approximately only half of patients undergoing treatment recover (IIIPE and CB, 2006).

Ieso Digital Health is a provider of Internet-enabled CBT (IECBT), where patients communicate with an accredited CBT trained clinician using a real-time text-based system. The clinical effectiveness of IECBT has been demonstrated in depression and other mental health conditions (Kessler *et al.*, 2009; Catarino *et al.*, 2018). However, many patients do not experience adequate symptom relief from existing first-line treatments – our own data indicate that approximately 50% of patients with mental health disorders experience treatment resistance to a standard course of IECBT, with similar rates reported elsewhere (IIIPE and CB, 2006; Tyrer and Baldwin, 2006). Understanding and overcoming barriers to improving treatment for common mental health conditions thus constitutes a vital goal, in order to provide the maximal therapeutic benefit to the largest possible numbers of people.

The link between behavioural biomarkers and mood is one that has been widely studied, with numerous research groups exploring the use of passively collected mobile-phone data to infer users’ mood (Ben-Zeev *et al.*, 2015; Asselbergs *et al.*, 2016; Lind *et al.*, 2018). Beyond being used as proxy measures of mood, some of these biomarkers also have a potential value as part of mobile mental health monitoring tools; for example, information derived from mobile phone location sensor data has been shown to be associated with symptoms of depression, bipolar disorder and schizophrenia (Saeb *et al.*, 2016; Palmius *et al.*, 2017; Fraccaro *et al.*, 2019).

While there is no doubt about the potential value and acceptability of mobile phone and wearable sensing in providing behavioural biomarkers of mental health, so far there have been very few controlled evaluations of how these data can be used to enhance the delivery and impact of mental health care (Torous, Staples and Onnela, 2015; Boonstra *et al.*, 2018). In their 2017 article, Ben-Zeev and colleagues describe CrossCheck, “a multimodal data collection system designed to aid in continuous remote monitoring and identification of subjective and objective indicators of psychotic relapse” (Ben-Zeev *et al.*, 2017). Other work has also demonstrated the value of passive mobile phone sensing for mental health monitoring, albeit in non-clinical populations (Ben-Zeev *et al.*, 2015; Lind *et al.*, 2018).

The current study aims to explore the value of activity trackers and mobile phone sensing in mental health monitoring, in a clinical population of patients with a diagnosis of depression or anxiety disorders. This study aims to investigate changes in passively collected cognitive and behavioural biomarkers, as the patient receives a course of IECBT, delivered by a qualified clinician. Furthermore, this is the first study to our knowledge exploring the potential value of sharing patients’ biomarker information with their therapist. We hypothesize the therapist can use this information to personalize the treatment being delivered to the patient, and thus improve clinical outcomes.

# Objectives

The primary objective of this research is to evaluate the value of passively collected cognitive and behavioural biomarkers as mental health monitoring tools. We aim to test the hypothesis that sharing patients’ biomarker information with their therapist, as the patient receives a course of cognitive behavioural therapy (CBT), can lead to improvements in clinical outcomes, through the delivery of more personalized treatment protocols.

The secondary objective of this research is to evaluate patient acceptability and engagement with mental health monitoring tools. Although research shows that patients are willing to consent to mobile phone data collection for mental health apps, they are less willing to consent with sharing personal data such as location and communication data. We hypothesize that providing value to the patient, through user-centred and user-informed design, will lead to higher acceptability rates for these types of tools.

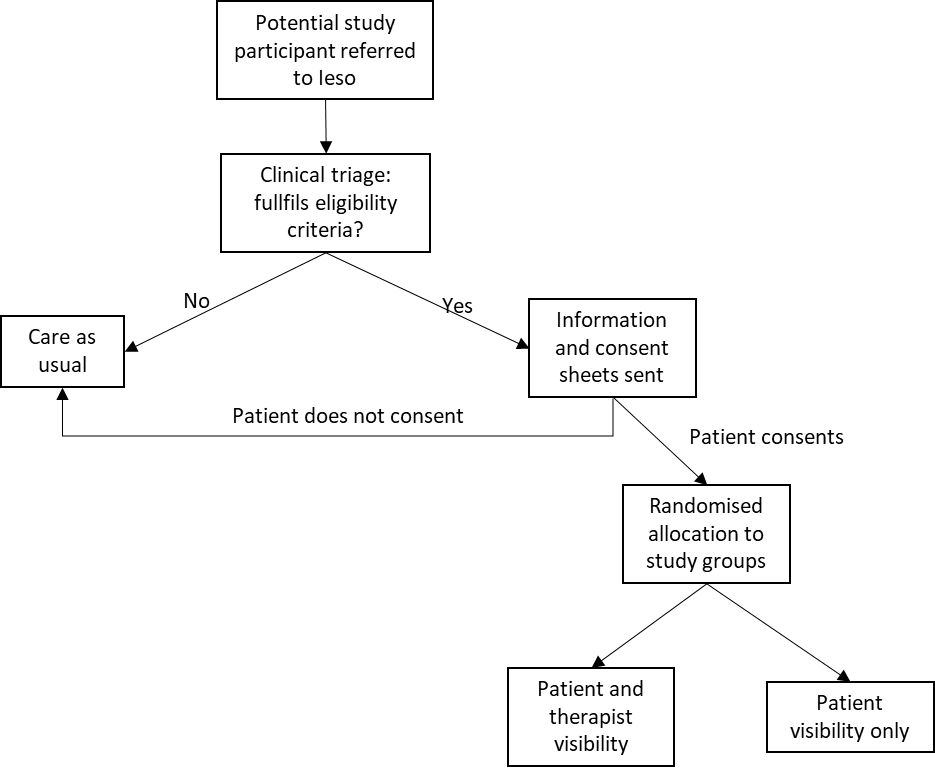
# Study design

Patients entering into the IECBT service in the normal course of treatment who fulfill eligibility criteria will be invited to participate in the research study, after being given time (at least 48h) to read the Information Sheets and ask any questions they wish of the research team. The same high quality of clinical care will be provided whether or not a given individual consents to participate in the study. Consenting patients will be randomized to one of two groups (Figure 1):

1. Therapist and patient visibility: Patients allocated to this group will be given a Fitbit and access to a mobile app that allows them to track their activity, location, social interaction and digital interaction biomarkers against their mood. They will receive a course of IECBT, and their therapist will also have access to these biomarkers and will use this information to tailor the care delivered to each patient and monitor patient outcomes.
2. Patient visibility only: patients allocated to this group will be given a Fitbit and access to a mobile app that allows them to track their activity, location, social interaction and digital interaction biomarkers against their mood. They will also receive a course of IECBT. However, their therapists will not have access to patients’ biomarker data.

Patients’ clinical outcomes and response to therapy will be monitored. Therefore, patients will be involved in the study for the duration of a course of therapy, which is typically between 8 and 12 weeks.

**Figure 1. Summary of flow for participant involvement in the study.**



## Clinical outcomes

The clinical outcomes collected in this study are collected as part of existing ‘standard of care’. In the context of this study treatment non-response will be defined as non-engagement or failure to achieve defined symptom change for recovery and/or improvement. The service provider, Ieso Digital Health, operates within the Improving Access to Psychological Therapies (IAPT) programme. As such, as mandated by IAPT, all patients receiving treatment, whether or not they have opted to participate in the study, will complete two symptom severity measures at initial assessment and before every therapy session: PHQ-9 (Kroenke, Spitzer and Williams, 2001) and GAD-7 (Spitzer *et al.*, 2006), corresponding to depressive and anxiety symptoms respectively. These metrics will be used to calculate clinical outcomes.

Within this framework, clinical outcomes including engagement, recovery and improvement will be defined following IAPT guidelines (Clark, 2011; Gyani *et al.*, 2013). Non-engagement will be defined as failure to attend at least two treatment sessions. This is the minimum dose of therapy a patient must receive such that pre- and post-treatment scores are collected and clinical change can be estimated (Gyani *et al.*, 2013).

Within the IAPT framework, clinical recovery and reliable improvement are calculated based on PHQ-9 and GAD-7 scores. Patients with two or more therapy sessions who show a significant reduction in at least one of the outcome measures from assessment to the last treatment session (i.e. decrease of six points or more in the PHQ-9 and/or four points or more in the GAD-7), while not showing a significant increase in the other outcome measure, were classed as showing reliable improvement.

If a patient scores eight points or above for GAD-7, and/or ten points or above for the PHQ-9, they will be classed as meeting the clinical threshold for caseness, which means they are considered to be suffering from clinically significant anxiety and/or depression symptoms. Patients with two or more therapy sessions who move from above caseness at assessment to below caseness at the last treatment session will be classed as recovered.

# Patient identification

Patients referred to the IECBT service for the treatment of depression or an anxiety disorder, who meet the eligibility criteria, will be invited to participate in the study.

## Inclusion criteria

* Patients must be over 18 years old at the time of recruitment and registered with a general practitioner in the geographical region where the service is commissioned and from where the study will recruit.
* Patients must have a primary diagnosis of depression or anxiety disorder.
* Patients must be able and willing to sign a consent form prior to the study.
* Patients must own an internet-connected mobile phone, running Android version 4.0.3 or higher.

## Exclusion criteria

* Patients who are not suitable for CBT, this includes patients with a comorbid diagnosis (a diagnosis of multiple disorders) of psychotic or personality disorder, autism spectrum condition or intellectual disability.
* Patients who display a significant risk of self-harm, as assessed by item 9 of the PHQ-9 questionnaire and ongoing assessment by their assigned clinician.
* Patients who have a poor likelihood of engagement with the therapeutic process, as assessed at triage.
* Patients who do not have access to an Internet enabled device or an Internet connection.
* Patients who have a low level of literacy. Patients who cannot write or read emails or texts will be excluded from this study because they will be unable to utilise the intervention.
* Patients who are visually impaired and are unable to write on or read from a computer and do not have access to appropriate assistive technology for the visually impaired.
* Patients who do not speak English.
* Patients who become unsuitable for treatment within an NHS primary care mental health (Improving Access to Psychological Therapy, IAPT) service. The normal NHS IAPT exclusion criteria will be applied whereby patients who become actively suicidal or present as a risk to others require a referral on to a more specialised, secondary care service. In addition, patients who are experiencing symptoms of psychosis, hyper-mania, severe cognitive impairment, severe personality disorder or severe learning disability are also deemed as being unsuitable for an IAPT service. These patients will be excluded from this study and referred on to more specialised services.
* We will exclude participants who are already involved in a different research project.

# Statistics and data analysis

## Sample size

This study aims to recruit a total of 200 patients completing a course of treatment, of whom 100 will be randomly allocated to standard psychotherapy with patient visibility of biomarkers, and 100 to enhanced psychotherapy, informed by patient and therapist’s visibility of biomarkers. A power analysis shows that a sample size of 100 engaged patients (i.e. patients who complete a course of treatment) per study group would be sufficient to detect a small between-groups effect size of approximately 0.40, with 80% power, and a medium effect size of approximately 0.46, with 90% power. This sample size is considerably larger than those of existing research on the use of mobile sensing technology for mental health monitoring (Ben-Zeev *et al.*, 2015; Asselbergs *et al.*, 2016; Saeb *et al.*, 2016; Palmius *et al.*, 2017; Lind *et al.*, 2018).

## Analyses

Summary statistics will be produced separately for all patients enrolled in the study and patients completing a course of treatment per protocol. Summary statistics for continuous variables will include N, mean, standard deviation and median. Tests for normality of the distribution will also be conducted. Summary statistics for categorical variables will include number and percent. Efficacy analyses will be conducted for engaged patients only.

Where appropriate continuous predictor variables will be scaled and centred to the mean. Multicollinearity analyses will be performed to investigate potential correlations between independent variables. Statistical significance will be defined as p<.05 two-tailed, uncorrected. All analyses will be performed in R (R Core Team (2019), 2019).

Primary analysis will be conducted on PHQ-9 and GAD-7 scores. These analyses will also be conducted on variables derived from PHQ-9 and GAD-7 metrics (i.e. recovery and improvement). For continuous variables (PHQ-9 and GAD-7 scores), a mixed model analysis of variance (ANOVA) will be conducted with time (pre- vs post-treatment) as a within-subject variable, and treatment group (therapist and patient visibility vs patient visibility only) as a between-subjects variable. These analyses will test the hypothesis that providing therapists with visibility of their patients’ biomarkers leads to a significant improvement in patients’ clinical outcomes, compared with providing visibility of biomarkers to the patient alone.

Similar analyses will be conducted on secondary outcome measures of daily mood ratings and behavioural biomarker data, including physical activity, sleep, geolocation, digital and social interaction. A mixed model analysis of variance (ANOVA) will be conducted with time (pre- vs post-treatment) as a within-subject variable, and treatment group (therapist and patient visibility vs patient visibility only) as a between-subjects variable. These analyses will test the hypothesis that providing the therapist with visibility of patients’ biomarkers leads not only to changes in clinical outcomes and daily mood, but also to changes in behavioural biomarkers being targeted as part of more personalized therapeutic interventions.

Correlation analyses between primary outcome measures (PHQ-9 and GAD-7) and secondary outcome measures (daily mood and behavioural biomarker data, as detailed above) will also be conducted. These analyses aim to test the hypothesis that certain passively collected biomarkers data may be highly correlated to mental health symptoms, and thus can be used as proxies for these measures in a system designed to passively monitor mental health status.

To control for the effect of covariate variables such as patient demographics and length of treatment (Catarino *et al.*, 2018), treatment group (therapist and patient visibility vs patient visibility only) will also be included as a between-subjects variable in a secondary ANCOVA analysis, with the demographic variables and number of treatment sessions included as covariates and time (pre- vs post-treatment) as a within-subject variable.

Growth curve modelling will be used to assess rate of change in primary and secondary outcome measures over time, and calculate the mean number of treatment sessions needed to reach the thresholds for the derived clinical outcomes variables for each group (i.e. mean number of sessions needed to reach recovery or improvement). Descriptive statistics for the mean recovery rate and improvement rate for each group will also be presented.

Finally, for categorical variables derived from PHQ-9 and GAD-7 scores (i.e. recovery and improvement), a chi-square analysis comparing study groups will be performed, to test the hypothesis that providing therapists with visibility of their patients’ biomarkers leads to a significant improvement in patients’ clinical outcomes, compared with providing visibility of biomarkers to the patient alone. To control for the effect of covariate variables on categorical outcome metrics, a logistic regression with covariate variables and treatment group as independent variables will also be conducted.

## Data management

Ieso Digital Health follows nationally and internationally recognised standards for information security (Cyber Essentials Plus, ISO 27001 and the 10 National Data Guardian standards self-certified via the NHS Data Security and Protection Toolkit, <https://www.iesohealth.com/en-gb/legal/iso-certificates>). All patient data are stored confidentially and securely within the Microsoft Azure cloud environment geolocated within the UK, configured and maintained by Ieso. In all study-specific data and documents, other than the signed consent, the patients will be identified by a unique study-specific number and/or code, not by name. Patients’ names and any other directly identifying details will not be included in any study data electronic files.

Direct access to the data will only be granted to authorised researchers or the Ieso clinical team; or if required by law, following at all times appropriate legislation and good governance procedures. Only aggregated de-identified data will be provided to the sponsor or funder for monitoring and/or audit of the study.

All research data including personal data held separately from your patient file will be held for a minimum of 20 years in accordance with Medical Research Council guidance. Personally identifiable data collected as part of routine practice (standard of care) shall be retained per standard clinical practice.

# References

**Asselbergs, J. *et al.*** (2016) ‘Mobile Phone-Based Unobtrusive Ecological Momentary Assessment of Day-to-Day Mood: An Explorative Study’, *Journal of medical Internet research*. doi: 10.2196/jmir.5505.

**Ben-Zeev, D. *et al.*** (2015) ‘Next-Generation psychiatric assessment: using smartphone sensors to monitor behavior and mental health’, *Psychiatric Rehabilitation Journal*. doi: 10.1037/prj0000130.

**Ben-Zeev, D. *et al.*** (2017) ‘CrossCheck: Integrating self-report, behavioral sensing, and smartphone use to identify digital indicators of psychotic relapse.’, *Psychiatric Rehabilitation Journal*. doi: 10.1037/prj0000243.

**Boonstra, T. W. *et al.*** (2018) ‘Using Mobile Phone Sensor Technology for Mental Health Research: Integrated Analysis to Identify Hidden Challenges and Potential Solutions’, *Journal of medical Internet research*. doi: 10.2196/10131.

**Catarino, A. *et al.*** (2018) ‘Demographic and clinical predictors of response to internet-enabled cognitive–behavioural therapy for depression and anxiety’, *BJPsych Open*. Cambridge University Press, 4(5), pp. 411–418. doi: 10.1192/bjo.2018.57.

**Clark, D. M.** (2011) ‘Implementing NICE guidelines for the psychological treatment of depression and anxiety disorders: the IAPT experience’, *International Review of Psychiatry*, 23(4), pp. 318–327.

**Fraccaro, P. *et al.*** (2019) ‘Digital biomarkers from geolocation data in bipolar disorder and schizophrenia: A systematic review’, *Journal of the American Medical Informatics Association*. doi: 10.1093/jamia/ocz043.

**Gyani, A. *et al.*** (2013) ‘Enhancing recovery rates: Lessons from year one of IAPT’, *Behaviour Research and Therapy*, 51, pp. 597–606. doi: 10.1016/j.brat.2013.06.004.

**Hunot, V. *et al.*** (2007) ‘Psychological therapies for generalised anxiety disorder’, *Cochrane Database of Systematic Reviews*. doi: 10.1002/14651858.CD001848.pub4.

**IIIPE, H. and CB, N.** (2006) ‘Emerging treatments for depression’, *Expert opinion on pharmacotherapy*. doi: http://dx.doi.org/10.1517/14656566.7.17.2323.

**Kessler, D. *et al.*** (2009) ‘Therapist-delivered internet psychotherapy for depression in primary care: a randomised controlled trial’, *The Lancet*, 374(9690), pp. 628–634. doi: 10.1016/S0140-6736(09)61257-5.

**Khan, A. *et al.*** (2012) ‘A systematic review of comparative efficacy of treatments and controls for depression’, *PLoS ONE*. doi: 10.1371/journal.pone.0041778.

**Kroenke, K., Spitzer, R. L. and Williams, J. B.** (2001) ‘The PHQ-9: validity of a brief depression severity measure.’, *Journal of general internal medicine*. Springer, 16(9), pp. 606–13. doi: 10.1046/j.1525-1497.2001.016009606.x.

**Lind, M. N. *et al.*** (2018) ‘The Effortless Assessment of Risk States (EARS) Tool: An interpersonal approach to mobile sensing’, *Journal of Medical Internet Research*. doi: 10.2196/10334.

**Lozano, R. *et al.*** (2012) ‘Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010’, *The Lancet*. doi: 10.1016/S0140-6736(12)61728-0.

**National Institute for Health and Clinical Excellence** (2011) ‘Generalised anxiety disorder and panic disorder in adults: Management’, *National Institute for Health and Clinical Excellence*.

**Palmius, N. *et al.*** (2017) ‘Detecting bipolar depression from geographic location data’, *IEEE Transactions on Biomedical Engineering*. doi: 10.1109/TBME.2016.2611862.

**R Core Team (2019)** (2019) ‘R: A language and environment for statistical computing.’, *Accessed 1st April 2019*.

**Saeb, S. *et al.*** (2016) ‘The relationship between mobile phone location sensor data and depressive symptom severity’, *PeerJ*. doi: 10.7717/peerj.2537.

**Spitzer, R. L. *et al.*** (2006) ‘A brief measure for assessing generalized anxiety disorder: the GAD-7.’, *Archives of internal medicine*, 166(10), pp. 1092–1097. doi: 10.1001/archinte.166.10.1092.

**Torous, J., Staples, P. and Onnela, J. P.** (2015) ‘Realizing the Potential of Mobile Mental Health: New Methods for New Data in Psychiatry’, *Current Psychiatry Reports*. doi: 10.1007/s11920-015-0602-0.

**Tyrer, P. and Baldwin, D.** (2006) ‘Generalised anxiety disorder’, *Lancet*. doi: 10.1016/S0140-6736(06)69865-6.

**Vos, T. *et al.*** (2016) ‘Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015’, *The Lancet*, 388(10053), pp. 1545–1602. doi: 10.1016/S0140-6736(16)31678-6.

**World Health Organisation** (2014) ‘Mental health : strengthening our response’, *Fact sheet N.220*. doi: 10.1037/e360882004-001.

**World Health Organization** (2011) ‘Mental Health Atlas 2011’, *World Health Organization*. doi: 10.1093/bja/aes067.