Battling Depression: From Clinical Development Strategies to Patient Perspectives

The fight against depression is challenged, not only by the insidious nature of the disease, but also by patients' own desperate desires to get better

Dr Thomas Thompson, Miaesha Campbell, Jill Adkins, and Joan Gushue at Medpace

According to WHO, depression is the leading cause of disability worldwide (1). Depression is a debilitating disorder that impacts physical health and wellbeing. In the US alone, it is estimated that 17.3 million adults had at least one major depressive episode, representing 7.1% of all US adults (2). Each year in Europe 25% of the population suffer from depression or anxiety, about 50% of major depressions are untreated, and up to 50% of chronic sick leaves are due to depression/anxiety (3). While there are effective treatments available, many patients need to try multiple medication regimens before they fully recover from their symptoms, and up to a third of people fail multiple attempts at treatment (4). Additionally, it is not uncommon for patients suffering from depression to be incorrectly diagnosed leading to a delay in treatment. Conversely, others who do not have depression may be misdiagnosed and prescribed antidepressants, which are ineffective.

The problem has been further exacerbated by the COVID-19 pandemic. In a recent Kaiser Family Foundation Tracking Poll, 53% of adults in the US reported that their mental health has been negatively impacted due to worry and stress over the coronavirus (5). Social isolation, financial stress, health concerns, and feelings of loss have all increased during COVID-19 – and that picture is repeated around the world.

Challenges and Considerations in Clinical Development for Depression

Clinical research is being conducted to further understand the disorder and to find better treatments. However, there

are unique complexities that need to be considered and planned for in order to be successful. In this article, we'll address some of the challenges of conducting clinical research in depression from an operations, medical, and patient perspective.

Operational Perspective: Tools and Best Practices for Site Engagement

Patients diagnosed with major depressive disorder require special considerations for recruitment and engagement. This includes a clinical operations model that is focused not only on the study treatment, but also ensuring that a support system is in place for each patient. Collaboration across medical experts and clinical trial management teams should address operational issues and ensure patient care options that educate and provide for the patient needs.

To successfully operationalise psychiatric studies, it is imperative that comprehensive study management plans are developed at the outset of study enrolment. These plans must focus on the timely execution of clinical trial enrolment and the safety of each patient, and must also address the unique challenges and opportunities of patients who have been diagnosed with clinical depression. This includes cultivating strong site relationships, having open communication, and a clear understanding of each site's capabilities and resources. This allows the CRO to customise support, including training, technology, and communication.

Alleviating site burden, while also supporting study enrolment and data integrity, is key. For example, technology can support site engagement by providing easy access to study documents and training videos for reference and monitoring oversight. Additionally, effective training for site staff enables them to continually educate participants on how their full participation is necessary to help the trial meet its objectives.

Clinical studies in depressive disorders generally require a large number of patient and clinician reported scales and outcome measures. There may also be a requirement for sites to designate separate safety raters and efficacy raters, which further increases operational complexity. Requirements for execution of scales and questionnaires should be clearly defined for site staff at the outset of the study, and robust training for raters should be provided to ensure these are administered the same way for each patient. Additionally,

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site materials should be provided in a manner that facilitates efficient administration of questionnaires in the proper order. Scales and questionnaires, which need to be completed on paper, should be provided to sites in a well-organised patient binder to avoid missed assessments, or assessments being completed in the incorrect order. Electronic clinical outcome assessment solutions should be considered where possible to decrease the administrative burden of transcribing scale responses onto case report forms. Consideration should also be given to the number of scales and questionnaires used in a study, as too many assessments can lead to patient fatigue and frustration, which may impact data quality.

A high percentage of clinical trials of antidepressant therapies do not meet their primary endpoint due to high placebo response rates. Much effort has been put into trying to understand study design factors, which can lead to an increase in placebo response, and to develop study designs, which can better control for this. However, operational planning in clinical trials for depressive disorders should also include implementation of strategies to minimise placebo response. It is not uncommon for patients to still maintain an expectation that their symptoms of depression will be improved by taking study medication, even though they may be receiving placebo. Patients may also seek to please study staff by providing what they perceive is the correct response to study questionnaires. In addition to site education on the factors which contribute to higher placebo response rates, consideration should be given to implementing a standardised script that is read to patients before completing efficacy assessments (6). The script should reinforce the fact that the patient may be receiving a placebo, and, as such, is not expected to have an improvement in their symptoms of depression. The script should also serve as a reminder that patients should respond accurately to rater questions, and not try to provide the response they believe the rater is hoping for.

Medical Perspective: Early and Ongoing Input

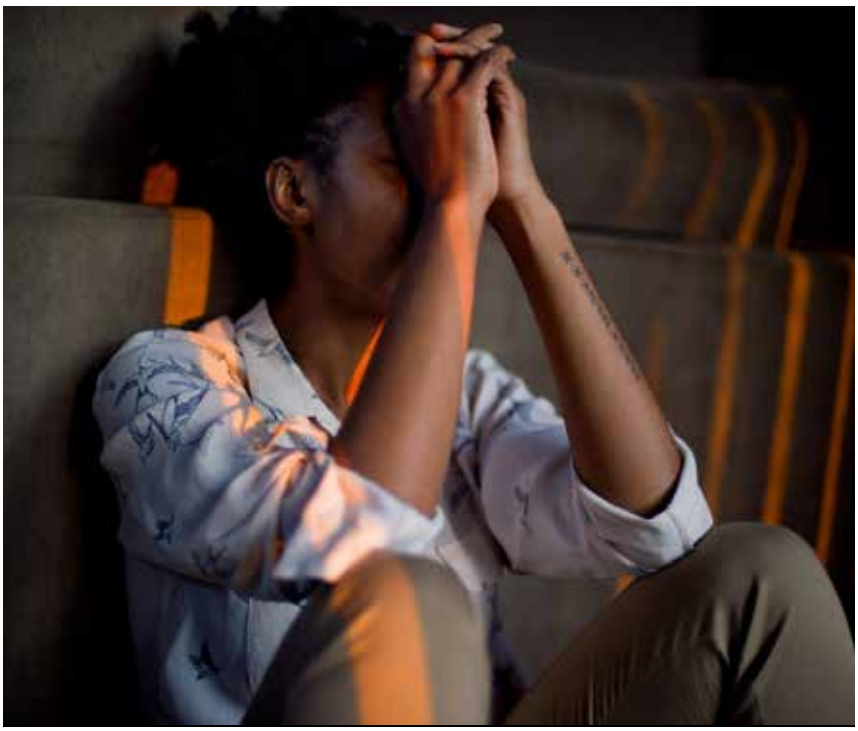
Medical expertise is critical to study success. Involving medical specialists with knowledge of psychiatric clinical development ensures the study is designed properly from protocol inception and development through to clinical study reporting. The medical expert can help evaluate and guide study design development and tailor it to the specific needs of a sponsor. Early protocol input and refinement ensures the end points and inclusion/exclusion criteria are carefully vetted to enrol the right patient in the study. Expert medical support translates scientific academic concepts into successfully operationalised trials.

Incorporating lessons learned though experience allows the clinicians and patients to have a positive experience in trial participation. This encourages continued research and education in the space. A real-world example is to avoid having a patient-reported and clinician-reported version of the same scale used in the study. Since the questions are nearly identical, this can contribute to patient frustration and irritation, and may detract from accurate endpoint collection. Solving this issue during protocol development ensures patients and clinicians are more accurately and efficiently collecting essential trial data.

Identification of the right patient for the trial is also key. Independent evaluation of patients confirming the eligibility criteria has been met during the screening period confirms that the illness is a specific state and excludes patients with symptoms that are non-specific or unrelated to the illness under study. Independent assessments of patients prior to randomisation optimises enrolment into the trial.

Patient Perspective: Making 'Patient-Centricity' More Than a Buzz Word

Most important is ensuring patient safety and providing the appropriate support for their clinical trial journey. This begins with a strong clinical operations team who understand



the nuances of treating patients with depression and can strategically position the study around the patient's needs.

For patients with depression, their condition interferes with daily life. People living with major depressive disorder often experience a loss of interest in activities, and changes in sleep, appetite, energy level, and concentration. It is difficult for them to keep up with their daily routine, and they can find themselves feeling isolated. Studies should implement programmes that partner with patient advocates to understand how the study will be perceived by patients, provide guidance on visit procedures that may be burdensome to patients, and educate patients about the study opportunity, their condition, study requirements, and provide information on where they can seek support. Educational tools include teaching videos for patients, websites that inform and engage, and reminders about study requirements.

Offering supportive services on the onset will help navigate the clinical trial experience. Some services include e-Consent, where patients can remotely consent to participate in a study. This is important for those looking for a way to join a trial but may have difficulty getting to a study centre. Studies for patients with depression are using new technology, such as telehealth 'virtual visits' that happen directly between sites/ healthcare providers and participants who may be unable to travel or attend an in-clinic visit. Other helpful services include transportation support to complete study visits at site, or offering nurses to come to a patient's home to complete vital assessments.

Patients struggling with depression may need support with remembering to take their study medication every day. Utilisation of a medication adherence app can increase patient compliance with taking their study medication by providing dosing reminders and providing prompt notification to sites about any missed doses so that study staff can quickly follow up with patients to address any issues or concerns.

Conclusion

Depression is a serious mood disorder and a leading cause of disability worldwide. Many sufferers do not seek treatment due to the stigma of the disease. Their lives are profoundly affected by their symptoms, which also impact the lives of their family and loved ones. We must continue to advance development of successful treatment options, while removing the stigma surrounding depression and mental health through education about the condition.

Clinical development for effective treatment options is more important than ever. There is a broad spectrum of research underway including antidepressant medications, psychotherapy, and brain stimulation therapies. Regardless of the approach, we need to always ensure that the patient's wellbeing and safety is the centrepiece of the study design and execution.

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Dr Thomas Thompson is a Medical Department Vice President at **Medpace**. Thomas is board certified in both psychiatry and geriatric psychiatry, and has over 20 years of Phase I-IV clinical development experience.

Miaesha Campbell is Director of Patient Recruitment at **Medpace** with over 13 years of experience overseeing patient recruitment and retention strategies and solutions for clinical trials.

Jill Adkins is a Director in Clinical Trial Management at **Medpace** with over 20 years of clinical research experience, with a particular interest in the development of treatments for neurological and psychiatric indications.

Joan Gushue is a Director in Clinical Trial Management at **Medpace** with over 15 years of clinical research experience, including eight years as a Clinical Trial Manager and seven years as a Clinical Research Associate.