Summary: ISCTM Psychedelics Working Group Session, 12 Sept 2024

The third and final in-person meeting of the ISCTM Psychedelics Working Group was attended by 82 conference registrants, including the co-chairs Amir Inamdar and Joyce Tsai, and the discussants Alex Kelman and Kevin Lanzo. Attendees were largely pre-assigned to discussion tables, based on their preferred discussion topics. Each of the 9 tables chose a discussion lead and a scribe. After 45 minutes of discussion, the table leads and scribes met with their assigned discussants during a short break, after which the discussants presented summary recommendations during the remainder of the time in the working group session.

The two questions under discussion were:

1) How to ensure and assess fidelity to a given psychological support model?
2) What are the challenges to scaling delivery of psychological support to large multi-site late-stage global studies?

Alex Kelman summarized the discussions on monitoring and measurement of fidelity to psychological support model employed in studies. Key points include:

- It is important to consistency with other processes employed in clinical trials. To achieve this consistency, both a training manual and certification of the manualized training are recommended.
- Different psychological support models exist based on different sponsors, the pharmacology of different agents under development and they hypothesized mechanisms of therapeutic action. Depending on the model, the psychological support might range from active therapist-led psychotherapy to session monitors who are present to observe the patient and ensure safety. The specific form of psychological support should be clearly defined by sponsors. Depending on the level of intervention, there may be more or less need for detailed and specific adherence criteria.
- There was a recommendation to video and audio record treatment administration ("dosing") sessions at a minimum. This is to ensure safeguarding of the patient against therapist misconduct, as knowledge of being recorded is a powerful deterrent against unethical behaviors. Depending on what is intended at pre-treatment and post-treatment, audio/video recording of those sessions is also recommended. Furthermore, it was recommended that the recordings be evaluated and archived by an independent 3rd party.
- In addition to archiving of recordings, it is important for sponsors to put in place a supervision process for study monitors/therapists during studies, to conduct checks for competence and good practice.
- Regardless of the psychological support model, session monitors should be trained and provided with the tools to take notes in a consistent format and level of detail. This will ensure proper data collection and evaluation of potential adverse events.

- The level of fidelity monitoring should be commensurate with the level of psychological support. Sponsors must clearly define adherence criteria appropriate to the psychological support model and consistent with the training manual.
- Actual evaluation of fidelity can be accomplished either via 3rd party human expert raters or via Artificial Intelligence. This could be done during the study or more commonly after study completion. Existing AI programs typically use audio recordings. The AI should be validated against assessments by expert human raters. While it may be preferable to evaluate fidelity in 100% of patients; assessment of a random sample may be acceptable for larger studies and more feasible.
- There is currently no specific regulatory requirement to measure fidelity to the psychological support model. However, such measurement is consistent with ensuring the quality of study conduct; and it is important to include the fidelity assessment in the NDA.

Kevin Lanzo summarized the discussions on scaling provision of psychological support for large late-stage clinical trials of psychedelics.

- Discussants noted that the FDA recommendation of having two session monitors, one of whom is a state-licensed therapist, in the room with the patient during psychedelic dosing sessions may be difficult to provide at scale and might not be necessary. The point of having two session monitors is to prevent abuse. However, that second monitor might reasonably be a video camera instead.
- Greater intensity of monitoring might be needed for a first administration of psychedelic drug to a naïve patient. Subsequent treatments at the same dose, however, might not require the same level of monitoring. Similarly, greater intensity of monitoring might be needed when the highest dose is administered, in studies that involve administration of multiple treatments at different doses (eg the Hopkins model, in which a lower initial dose is followed by a subsequent higher dose.)
- It was noted that payers are unlikely to be willing to pay for the presence of two attendants for each patient for the duration of a psychedelic dosing session that might be as long as 12 hours (in the case of LSD). Therefore, sponsors have a strong incentive to optimize and streamline session requirements without compromising on safety.
- The need for a state-licensed therapist was questioned for drugs/studies that do not actually require psychotherapy. For studies in which psychological support is meant to support patient safety and not delivery of psychotherapy, a state-licensed HCP (eg. psychiatric nurse) should be sufficiently qualified, and can be trained on the specific psychological support model. In some respects, a nurse with psychiatric experience may be preferable in some situations as he/she would bring the clinical judgment to know when a medical intervention may be necessary.
- One of the biggest bottlenecks in scaling for larger studies in training and providing therapists/monitors to staff the dosing sessions. Reducing the required number of in-room monitors to one, and allowing licensed nurses with appropriate psychiatric experience and certified training in the psychological support model (for studies that do

not involve psychotherapy per se) could go a long way toward alleviating that staffing bottleneck.

- Based on post-marketing examples of esketamine administration, group dosing in ward situations should also be investigated. Such a dosing model would further streamline resource utilization while maintaining necessary patient observation and provision of support to patients when needed.
- The working group urged industry sponsors to agree on a basic standard training program for session monitors and suggested a streamlined training process that utilizes a library of videos of dosing session with different drugs and illustrating different patient scenarios. These videos would potentially supplant current requirements by some sponsors for in-person observation as part of training and qualification of session monitors.