Methodological Issues in Study Designs for Clinical Trials with Psychedelics

Working Group 2 – operational challenges faced by sites and sponsors, and psychological support in psychedelic studies.

Summary of 21 Feb 2024 Discussion

This working group meeting was designed as a workshop. Each attendee was assigned to one of eight table-based discussion groups based on his or her indicated interest in one of 4 discussion topics, which were:

1. What are the operational challenges that clinical research sites face in preparing for and participating in clinical trials of psychedelic compounds?
    a. How are these challenges similar or unique for different psychedelic compounds and psychiatric disorders?
    b. What are some best practices?
    c. What are CROs/Sponsors doing well, and what changes would you request from the CRO and/or Sponsor?

2. What are the operational challenges that CROs and Sponsors face in planning and management of clinical trials for psychedelic compounds?
    a. How are these challenges similar or unique for different psychedelic compounds and psychiatric disorders?
    b. What are some best practices?
    c. What are Clinical Research Sites doing well and what changes would you request from Investigators and Sites?

3. There are large differences in the psychological support models being implemented for studies in different compounds and by different Sponsors. These range from “psychedelic assisted psychotherapy” to limiting therapists to a “chaperone” role during the dosing session. For the clinical evaluation of a drug:
    a. Is there agreement that some form of psychological support framework is necessary for treatment with psychedelics?
    b. Is meeting with a therapist prior to and after receiving study drug for “psychological support” necessary – what is the purpose of these pre/post meetings?
    c. What is the minimum necessary interaction between participant and therapist prior to dosing?
    d. What is the minimum necessary interaction between participant and therapist after dosing?

4. How do we ensure that therapists engage with study participants in a consistent manner as described in the study protocol or study-specific therapist manual; and

how do we measure their performance and the impact of their performance on study outcomes?

a. Who reviews therapist performance and when should this be done?
b. Is there a role for remediation training during an ongoing study?
c. How should we measure fidelity to the protocol / therapist manual?
d. Are there analyses of measured fidelity ratings that can inform as to potential therapist influence on outcomes, or does a factorial study need to be performed?

One volunteer from each table moderated the discussion and presented the groups thoughts, conclusions, and recommendations to the full working group at the end of the discussion period.

Site Challenges: Tables 1 and 8

Identified challenges included study complexity, expense, lack of qualified staff, space requirements, regulatory hurdles, dealing with both staff and patient expectations, and difficulties in recruiting and retaining patients.

- Studies are more expensive for sites to undertake because of the complexity of the studies, which require more site staff to coordinate multiple interactions between sites, patient, investigator, 3rd party raters, therapists, and vendors, and which also require dedicated drug administration space. Most sites are not used to the level of complexity required for psychedelic studies. For studies of classic psychedelics, it is possible to dose only 1 patient/day. That patient requires the dedicated space and therapists for a full day; and a physician must also be immediately available on call and review the patient at the end of the dosing day to review AEs and authorize discharge home. Patients can only be discharged to a carer/helper.
- Lack of qualified staff: In addition to high quality study investigators and coordinators, the psychedelic studies require 2 facilitators/chaperones, at least 1 of whom must be a qualified / licensed therapist/ HCP, to dedicate their entire day on the day of dosing. The primary therapist must also commit to meeting the patient on the day prior to dosing and the day afterward. Such therapists are not generally full-time site staff. They are not easy to find, after which they must be specifically trained for each study. It is not always clear (or differs by sponsor) what the specific role of the therapist is meant to be.
- Training of the facilitator/chaperone is particularly expensive and time consuming. But given the personnel resource demands of studies, sponsors should not limit the number trained to less than therapists per site.
- AE coding and discharge criteria are not always sufficiently clear. These also differ between sponsors.

- Space: A dedicated dosing room must be set aside for this purpose, and can accommodate only 1 patient/day.
- Managing site staff and patient expectations is a challenge. Specifically, how to tolerate 8+ hrs on placebo!
- Trying to maintain the blind is another unrealistic challenge. Even though the lead therapists are not raters, and no raters are present in the dosing session or post-dose follow-up sessions with the therapist, the reality is that patients talk. It will be clear to both patient and therapist if there is or is not a psychedelic experience during dosing. Afterward, patients have been reported to talk to the blinded 3rd party rater about their experiences, even though they are not asked to.
- Regulatory challenges: Psychedelics are schedule 1 substances. Sites must obtain DEA licenses for each drug and each study. This means time, paperwork, infrastructure (to obtain and install the required drug storage safe), state inspections, and the financial and personnel costs to navigate through the necessary processes.
- Patient recruitment challenges: Psychedelic studies are a hot topic and sites must do extensive prescreening to identify and exclude potential study participants who are essentially psychedelic-seeking rather than treatment seeking. Medical records may be helpful in identifying patients but in the US, these are extremely difficult to obtain.
- Patient retention challenges: long-term followup is needed. It's very hard to keep patients in a study after they received placebo, or even after they receive the active drug. Having an open-label treatment phase is highly recommended.

Sponsor/CRO Challenges: Tables 2 and 9

Identified challenges included site identification and preparation, IP management, and maintaining consistency of study conduct.

- Site identification: There are only so many sites with the capability to recruit the target psychiatric populations and conduct psychedelic studies. With the number of sponsors/studies current active, we may have reached a saturation point in terms of how many sites are realistically prepared to do psychedelic studies and how many different studies each site can conduct at one time.
- It is costly, time intensive, and risky to bring on inexperienced sites and prepare them to the point of readiness. Sites expressed a desire for sponsors and CROs to do more in terms of training new investigators/sites.
- Site preparation: Related to the above, it is challenging to set up sites in multiple geographic regions and prepare them for study participation, given regulatory/ethics hurdles, site inexperience, licensing requirements, as well as IP management hurdles.

- IP management hurdles: In addition to the bureaucracy involved in the export/import of schedule 1 controlled substances internationally, only so much drug can be kept onsite at any time; this increases the burden of IP management. Sponsors must also ensure that sites keep strict drug accountability records, in some cases even when transporting drug from the site pharmacy where drug is kept to the dosing room where drug is administered.
- Ensuring consistency of therapist/facilitator practice is a challenge given that many sites conduct more than one psychedelic study with more than one sponsor, at any given time. Each sponsor has a different patient population as well as a different therapist manual and distinct approach to the role of the therapist, ranging from being minimally interventional (being a chaperone during the drug administration session) to providing psychotherapy. Yet is it likely that the same therapists are involved in each site's studies, a situation that can lead to inconsistencies in practice. Therefore sponsors and CROs are challenged to ensure that their studies are conducted as intended. (underscores the need for a uniform minimum standard/ requirement for therapists/ psychological support)
- There isn't a 'one size fits all' for different psychedelics and approach needs to be adapted based on the psychedelic under study.

Psychological Support: Tables 3, 4, and 5

Discussion focused on the purpose of psychological support; and there was some consensus on what would be minimally necessary and expected. The point was made that in the practice of medicine it is always considered good practice for the clinician who administers any intervention, to meet with the patient beforehand and afterward.

- "Neutral" nomenclature was recommended, per earlier Working Group discussion on Zoom. Meetings with therapist prior to dosing, commonly referred to as "preparation" would be considered clinical visits prior to drug administration (pre-dose visits); and those after dosing, commonly referred to as "integration" would be considered clinical visits in follow-up to drug administration (post-dose visits). This neutral nomenclature would be agnostic to the specific interactions between clinician and patient, as these differ according to sponsor.
- The purpose for psychological support can vary by sponsor, study, disease state, and intention. To answer the question, one must as what is the study trying to interrogate. Is the question being asked about efficacy of the drug alone or adjunctive to psychological therapy?
- There is a tradeoff in considering how much to educate patients prior to an investigational intervention. The tradeoff is between safety/comfort and introduction of bias. Studies must balance sufficient safety while minimizing potential bias.

- Other considerations might be what sponsors seek, and what regulators would allow or require, to be in a drug label.
- One agreed purpose for having meetings prior to and post-treatment, is to provide a minimum level of psychological safety. From this standpoint, could be considered "necessary" although rigorous proof of such would theoretically require a 3-arm semi-factorial study.
- Meeting with the clinician prior to treatment is necessary to provide sufficient psychoeducation, set patient expectations, provide the patient with tools for emotional regulation that might become necessary during a psychedelic experience, and allow the patient to develop trust in the lead clinician who will monitor the drug administration session.
- Meeting with the clinician after treatment is to allow for a debrief, to give patients a safe space in which to digest their experiences, and to give the clinician an opportunity to observe the patient for emergent psychological sequelae.
- Standard clinical practice is for any physician/HCP who administers an intervention to meet with the patient prior to that intervention and again afterward in a follow-up visit. It would not be any different if the intervention is the administration of the psychedelic drug; the clinician would be expected to meet with the patient before and after the administration session.
- At least 1-2 hours is recommended pre-dose; and at least 1 meeting should be in person. Similarly, at least 1 hour is needed post-dose.
- Whether more time pre/post is needed depends on the patient, dose administered, and the indication under study. It is recommended that protocols allow for some flexibility for additional time, beyond the minimum if needed.
- At minimum, post-treatment followup might be as minimal as a checklist. Minimizing the follow-up visit to the absolute minimum necessary for safety would be another way of minimizing bias.
- Meeting with the patient before and after treatment allows development of rapport between patient and clinician, that could be important for patient safety. Furthermore, such rapport may help to improve study retention and protocol adherence.

Fidelity: Tables 6 and 7

The focus of discussion revolved around what constitutes fidelity, why sponsors would measure it, and how it might be accomplished.

- To define fidelity, we need a structure with agreed guidance and nomenclature. Simply put, fidelity could be defined as adherence to the guidance or manual provided to the monitors/ therapists.
- A key question is to what purpose is the assessment of fidelity necessary? Is it required by the sponsor to ensure consistent study conduct as required by the

protocol or is it required by regulators to ensure that results are not biased by lack of fidelity?

- The point was raised that a therapist/HCP's fidelity to the facilitator/chaperone role as required by the sponsor in psychedelic studies, should be no different that consideration of rater fidelity in any psychiatry study. Specifically, regulators trust that clinician rated scales for the primary efficacy measure can be performed without a separate fidelity measurement, if sponsors demonstrate that all raters were trained and qualified per their requirements.
- Despite the point above, it is also the case that regulators have questioned the role of psychological support in psychedelic studies; and they are clearly concerned that with the potential for unblinding in such studies, such unblinding can bias outcomes. Defining and measuring fidelity of the delivery of psychological support may help to address concerns regarding such potential bias.
- The question then becomes how to measure fidelity, in a very practical sense. Because sessions between therapist and patient are audio and/or video recorded, it was suggested that an AI approach could be applied to reviewing recordings.
- It was further suggested that sponsors of psychedelic studies might look to the psychiatric community's experience in rater training, qualification, and monitoring, to learn best practices in evaluation of fidelity. (work with the algorithms working group at the ISCTM)