JAMA Psychiatry | Special Communication

Modifying Informed Consent to Help Address Functional Unmasking in Psychedelic Clinical Trials

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IMPORTANCE There is unprecedented clinician, industry, and patient interest in the therapeutic development of psychedelic drugs. This is due to a combination of promising clinical trial results, positive media coverage, and the lack of novel pharmacologic treatments for psychiatric disorders in recent decades. However, the field faces a key methodological challenge: masking participants to treatment conditions in psychedelic clinical trials has been largely unsuccessful.

OBJECTIVE When participants can tell whether they received active drug or placebo, their responses to clinical assessments, questionnaires, and even their functional imaging and biological data can be influenced by preconceptions about treatment effects. Positive patient expectancies combined with ineffective masking may skew outcomes and inflate effect sizes. This complicates efforts to determine the safety and efficacy of psychedelic drugs. Here, we explore a method to help address this problem: modifying informed consent to obscure information about the study design.

EVIDENCE REVIEW We reviewed all contemporary (2000-2024) clinical trials of psychedelic or methylenedioxymethamphetamine (MDMA) therapy and corresponded with the investigators to compile information on the use of modifications to informed consent in these studies.

FINDINGS Modifying informed consent to obscure details of the study design has been implemented in several psychedelic clinical trials and may offer a way to strengthen masking. However, this approach poses significant ethical risks. We examine examples of modifications used in the psychedelic literature, discuss the current regulatory landscape, and suggest strategies to mitigate risks associated with modified informed consent.

CONCLUSIONS AND RELEVANCE Incorporating modified informed consent in future psychedelic clinical trials may improve interpretability and impact, but this has not been explicitly tested. Modifications to informed consent may not be appropriate in all cases, and risks to participants should be minimized by implementing appropriate guardrails.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2024.4312
Published online January 8, 2025.

Supplemental content

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Double-masked, randomized clinical trials (RCTs) of high doses of psychedelics (eg, psilocybin) or related drugs (eg, methylenedioxymethamphetamine [MDMA]) combined with psychotherapy[1] have demonstrated rapid, large, and sustained clinical improvements in multiple conditions, including depression,[2,3] posttraumatic stress disorder (PTSD),[4] and alcohol use disorder.[5] However, these RCTs are likely double-masked in name only, as the intense perceptual and psychological experiences induced by psychedelics[6] make effective masking challenging.[7] A meta-analysis found that the few psychedelic RCTs that measured masking success were effectively open-label, with 94% to 100% of participants correctly identifying that they received the active psychedelic treatment vs a nonpsychedelic placebo,[8] an issue highlighted by the US Food and Drug Administration (FDA) advisory panel when evaluating MDMA therapy for PTSD.[9]

Unmasking is not a new issue,[10] and there is debate about drawing special attention to it in psychedelic RCTs.[11] For example, a meta-analysis of selective serotonin reuptake inhibitor (SSRI) RCTs between 2000 and 2020 revealed that participants frequently guess their treatment assignment well above chance levels.[10] While other psychoactive drugs can be difficult to mask, the risk of functional unmasking usually increases over the period of chronic administration, whereas the acute subjective effects of high-dose psychedelics typically lead to immediate functional unmasking. Further, unmasking is more likely to extend to study staff in psychedelic RCTs, as the drug is usually administered under supervision, allowing staff to observe participants' responses.[10,12] Masking challenges are also compounded by the optimism surrounding psychedelic drugs, including enthusiastic media reports,[13] high-profile scientific publications,[2-5] and the FDA granting breakthrough therapy designations for at least 5 psychedelic treatments.[14] In this climate, participants in psychedelic RCTs often expect dramatic benefits,[15] which can heighten placebo responses if participants feel confident they received the active treatment[16] or provoke disappointment and nocebo responses if they believe they received an inactive treatment.[17] The combination of positive expectations and masking failure has

likely inflated effect sizes in psychedelic RCTs,[18] raising the risk that research findings are not meaningfully useful to patients, clinicians, researchers, or policymakers.[19]

Innovative RCT designs have been developed to manage placebo response rates. For example, the sequential parallel comparison design removes placebo responders in an unbalanced randomized lead-in phase before rerandomizing nonresponders in the second phase.[20] While this can reduce placebo response rates, it does not address the key issues in psychedelic RCTs, such as ineffective masking. Relatedly, the design does not counter nocebo effects; participants who receive an inactive placebo in psychedelic RCTs (and likely know it) demonstrate smaller treatment responses than participants who receive an inactive placebo in SSRI RCTs.[21] Alternatives to RCTs such as mechanistic and longitudinal studies, in which placebo responses are expected to wash out,[22] have also been proposed to address these challenges. Some have even suggested deemphasizing the goal of disentangling pharmacological and extrapharmacological influences on treatment outcomes altogether.[11] While multiple methodological approaches are undoubtedly essential for advancing psychedelic research, double-masked RCTs remain the gold standard for regulatory approvals of new pharmacological treatments. Thus, strategies to attenuate the influence of expectancy and improve masking in psychedelic RCTs are critically needed.

Defining Modified Informed Consent

Institutional review boards (IRBs) evaluate RCTs based on the American Psychological Association (APA) Code of Ethics,[23] Belmont Report,[24] and federal guidance (45 CFR 46),[25] which were developed to address multiple instances of unethical investigator behavior, including deception of participants that caused significant harm, particularly to marginalized communities.[26,27] Informed consent is now a central ethical principle of all research with human participants, but it can also contribute to unmasking in RCTs. During standard consenting procedures for pharmacological RCTs, participants learn about the goals and structure of the study, probabilities of being randomized to each treatment arm, and possible dosages and adverse effects of each and any drug they may receive. This knowledge, combined with experiences during the trial, can lead to strong beliefs about which treatment was administered. For example, a participant is informed that they could be randomized to receive either a high dose of a psychedelic or a nonpsychoactive placebo. Subsequently, the presence or absence of psychoactive effects may induce the belief that they did or did not receive the psychedelic and lead to expectations influencing study results. One method to possibly address this challenge is to modify informed consent to obscure features of the study design from participants and study staff.[28] Without this information, correctly guessing treatment allocation should be more challenging.

Regulatory Guidance About Modifying Informed Consent

The APA Code of Ethics and Belmont Report provide guidance on modifying informed consent in this way, each considering the following criteria:

- Lack of alternatives: Both agree that modifications can be justified only if more transparent procedures cannot accomplish the goals of the research.
- Study value: Both agree that modifications must be justified by the "study's value," typically interpreted to mean that the possible benefits of the study to society and patient health outweigh the risks of modification.[28]
- Debriefing: Both specify that studies that modify informed consent must have an adequate plan for disclosing any information that was misdescribed or withheld "when appropriate" as well as distributing "research results" to participants. "When appropriate" has been interpreted to mean when it will not cause harm,[29] or if the information withheld/obscured is so inconsequential that no potential benefit could be gained from disclosure. David Wendler, PhD, a bioethicist at the National Institutes of Health; the Belmont Report; and the APA guidelines all recommend that participants should also be empowered to withhold their data if they are uncomfortable with what they learn during the debriefing process.
- Risk: The APA guidelines consider studies eligible for modified informed consent only if they are minimal risk: that is, "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[25] Pharmacological RCTs are never considered minimal risk and therefore could never modify informed consent per APA guidelines. In contrast, the Belmont Report states modifications can be permitted when "there are no *undisclosed risks* to subjects that are more than minimal" (emphasis added). Thus, pharmacological RCTs could modify informed consent if the modifications do not interfere with disclosure of all meaningful risks to participants.

An analysis of the bioethical landscape of RCTs offers further guidance about this issue.[28] While there is scarce bioethical discussion of modifying informed consent to improve masking in particular, the literature on modifying informed consent for other purposes is plentiful. Wendler is aligned with the Belmont Report; if an RCT meets the other 3 criteria (lack of alternatives, study value, debriefing), modification may be ethical in greater than minimal risk studies as long as all greater than minimal risks are disclosed.[28] Additionally, Wendler notes most regulations and bioethicists require that participants are provided with the following "essential information" in order to consent: (1) the purpose of the research, (2) the major procedures, (3) the significant risks and potential benefits, (4) the alternatives, and (5) the fact that participation is voluntary.[28] However, what counts as essential information is debated. The Belmont Report proposes that researchers should disclose the information that a "reasonable volunteer" would want to know,[24] while some bioethicists argue that any information that participants might regard as worthy of consideration in the process of deliberation,[30] or all and only the information that would influence whether potential participants decide to enroll,[31,32] should be disclosed. Importantly, if all greater than minimal risks are communicated to participants, serious adverse events should never arise in relation to aspects of a study that were not disclosed.

In our and our colleagues' experience, many IRBs take the more conservative approach consistent with the APA guidelines, rarely, if ever, approving modified informed consent in greater than mini-

mal risk trials, including psychedelic RCTs. However, IRBs at some institutions have approved modified informed consent in psychedelic trials (**Table**).[6,33-42] This variability is consistent with findings that IRBs differ in their application of federal regulations, making

Table. Modifications to Informed Consent in Contemporary Psychedelic Clinical Trials

Source	Population	Study procedures (what occurred)	Information provided to participants	Modified informed consent description[a]	Masking assessed[b]
Griffiths et al,[6] 2006	n = 36 HC	• Double-masked, randomized, crossover[c] • n = 30 Completed 2 dosing sessions: received psilocybin (30 mg/70 kg) and MPH (40 mg/70 kg) in counterbalanced order • n = 6 Completed 3 dosing sessions: received MPH (40 mg/70 kg) in first 2 dosing sessions, followed by unmasked psilocybin (30 mg/70 kg) in session 3	Participants were told they would complete 2 or 3 dosing sessions. In ≥1 session, they would receive moderate- or high-dose psilocybin. In other sessions, they could receive inactive PL, low-dose psilocybin, or variable doses of other drugs (DXM, nicotine, diphenhydramine, caffeine, MPH, amphetamine, codeine, alprazolam, diazepam, triazolam, or secobarbital).	1. Arms and chances: possibility of receiving 11 different interventions was raised; only 2 interventions (psilocybin, MPH) were possible. 2. Drugs and/or dosages: specific dosages of psilocybin (30 mg/70 kg) and MPH (40 mg/70 kg) were withheld. 3. Placebo features: presence of the active PL control (MPH) was withheld.[d]	No
Carbonaro et al,[33] 2018	n = 20 HC	• Double-masked, randomized, crossover • All participants completed 5 dosing sessions: received PL, psilocybin (10, 20, and 30 mg/70 kg), and DXM (400 mg/70 kg)	Participants were told they could receive PL or doses of 38 psychoactive drugs from a variety of drug classes, including psilocybin and DXM. In ≥1 session, they would receive a classic hallucinogen or a dissociative anesthetic hallucinogen.	1. Arms and chances: possibility of receiving 38 different interventions was raised; only 3 interventions (PL, psilocybin, DXM) were possible. 2. Drugs and/or dosages: specific dosages of psilocybin (10, 20, and 30 mg/70 kg) and DXM (400 mg/70 kg) were withheld. 3. Placebo features: intent of active PL control (DXM) was withheld.	Yes[e]
Reckweg et al,[34] 2021	n = 22 HC	• 2 Open-label arms • n = 18 Completed 1 dosing session: received 5-MeO-DMT (2, 6, 12, or 18 mg) • n = 4 Received up to 3 increasing doses of 5-MeO-DMT (6, 12, and 18 mg) at 3-h intervals within a single dosing session based on achievement of "peak experience"	Participants were told they would receive a "tryptamine psychedelic" but not specific entity or dosage. Extensive information provided regarding possible drug effects, duration, and potential adverse events. Debriefing: on study completion, participants were told they received 5-MeO-DMT and the dosage.	2. Drugs and/or dosages: Identity of psychedelic drug (5-MeO-DMT), and specific dosages (2, 6, 12, or 18 mg) were withheld.	No
Bedi et al,[35] 2010	n = 21 HC	• Double-masked, randomized, within-participant • All participants completed 4 dosing sessions: received MDMA (0.75 and 1.5 mg/kg), MA (20 mg), and PL	Participants were told they could receive a "range of possible drugs." No additional information was reported. Debriefing: on study completion, participants "were fully debriefed."	1. Arms and chances: possibility of receiving multiple drugs was raised, but only MDMA, MA and PL were possible. 2. Drugs and/or dosages: identity of drugs and specific dosages of MDMA (0.75 and 1.5 mg/kg) and MA (20 mg) withheld. 3. Placebo features: intent of active PL control (MA) was withheld.	Yes
Bershad et al, 2019[36] and 2024[37]	n = 36 HC	• Double-masked, randomized, within-participant • All participants completed 4 dosing sessions: received MDMA (0.75 and 1.5 mg/kg), MA (20 mg), and PL	Participants were told they could receive a stimulant such as MDMA or MA, a sedative such as valium, a cannabinoid such as marijuana, or PL. Debriefing: on study completion, participants were told they received MDMA, MA, PL, and the dosages.	1. Arms and chances: possibility of receiving multiple drugs was raised, but only MDMA, MA, and PL were possible. 2. Drugs and/or dosages: specific dosages of MDMA (0.75 and 1.5 mg/kg) and MA (20 mg) were withheld. 3. Placebo features: intent of active PL control (MA) was withheld.	Yes
Molla et al,[38] 2023	n = 37 HC	• Double-masked, randomized • n = 18 Completed 2 dosing sessions: received MDMA (100 mg) and PL • n = 19 Completed 2 dosing sessions: received MA (20 mg) and PL	Told capsules might contain a PL, a stimulant such as amphetamine or MDMA, a sedative, or a hallucinogenic drug.	1. Arms and chances: possibility of receiving multiple drugs was raised, but only MDMA, MA, and PL were possible. 2. Drugs and/or dosages: identity of stimulant drugs (MDMA and MA) and specific dosages of MDMA (100 mg) and MA (20 mg) were withheld. 3. Placebo features: intent of active PL control (MA) was withheld.	Yes

(continued)

Table. Modifications to Informed Consent in Contemporary Psychedelic Clinical Trials (continued)

Source	Population	Study procedures (what occurred)	Information provided to participants	Modified informed consent description[a]	Masking assessed[b]
Griffiths et al,[39] 2016	n = 51, Cancer diagnosis and anxiety/ mood symptoms	• Double-masked, randomized, crossover • n = 25 Completed 2 dosing sessions: received low-dose psilocybin (1-3 mg/70 kg) followed by high-dose psilocybin (22-30 mg/70 kg) • n = 26 Completed 2 dosing sessions: received high-dose psilocybin (22-30 mg/70 kg) followed by low-dose psilocybin (1-3 mg/70 kg)	Patients were told they would receive psilocybin in both dosing sessions, dosages may range from very low to high, dosages may or may not be the same in both sessions, individual sensitivity varies, and ≥1 dose would be moderate to high.	2. Drugs and/or dosages: specific dosages of psilocybin (1-3 mg/70 kg, 22-30 mg/70 kg) were withheld. 3. Placebo features: both doses were suggested to be psychoactive, while 1-mg dose was not expected to be.	No
Ot'alora et al,[40] 2018	n = 28, PTSD	• Double-masked, randomized • 1:1:2 Randomization (40:100:125 mg)[f] • n = 6 completed 2 dosing sessions: received "comparator" dose MDMA (40 mg) twice • n = 9 Completed 2 dosing sessions: received "active dose" MDMA (100 mg) twice • n = 13 Completed 2 dosing sessions: received active dose MDMA (125 mg) twice	Patients were told they would complete 2 dosing sessions with an active dose of MDMA or a comparator that may have MDMA in it (no details provided about chance that comparator has MDMA in it; possible MDMA dosages not provided). Patients were told there was a 78% chance of receiving active dose of MDMA and a 22% chance of receiving the comparator. Debriefing: Drug identities and dosages disclosed ~1 mo after second dosing session.	2. Drugs and/or dosages: specific dosages of MDMA (40, 100, 125 mg) were withheld. 3. Placebo features: identity of the comparator (MDMA, 40 mg) was obscured.	Yes
Carhart-Harris et al,[41] 2021	n = 59, Depression	• Double-masked, randomized, therapy-assisted • n = 30 Completed 2 dosing sessions: received psilocybin (25 mg) twice plus daily PL • n = 29 Completed 2 dosing sessions: received low-dose psilocybin (1 mg) twice plus daily escitalopram (10 mg for 3 wk, then 20 mg)	Patients were told they would receive psilocybin twice, but dosage could differ between sessions and could range as high as 25 mg in each session. There was a 50% chance of receiving daily escitalopram, the dose of which doubled after week 3 to become a clinically advised dose of 20 mg daily. Otherwise, patients would receive daily inert PL rather than escitalopram. (Not in methods; written communication with R.C.H., September 27, 2023.)	1. Arms and chances: not told there were 2 arms in study. 2. Drugs and/or dosages: told psilocybin dosage would vary, but in fact only 1 mg or 25 mg were possible. Patients were not told that those receiving the SSRI could only receive inactive dose of psilocybin.	No
Reckweg et al,[42] 2023	n = 16, Depression	• 2-Open-label arms • n = 8 Completed 1 dosing session, where they received 5-MeO-DMT (12 and 18 mg) • n = 8 Received up to 3 increasing doses of 5-MeO-DMT (6, 12, and 18 mg) within a single session based on achievement of "peak experience"	Patients were told they would receive a "tryptamine psychedelic" but not the specific entity or dosage. Extensive information was provided regarding possible drug effects, duration, and potential adverse events. Debriefing: at study completion, patients were told they received 5-MeO-DMT and the dosage.	2. Drugs and/or dosages: identity of psychedelic (5-MeO-DMT) and specific dosages (6, 12, 18 mg) were withheld.	No

Abbreviations: PL, placebo; HC, healthy control; DXM, dextromethorphan; MDMA, 3,4-methylenedioxymethamphetamine; MPH, methylphenidate; MA, methamphetamine; PTSD, posttraumatic stress disorder; SSRI, selective serotonin reuptake inhibitor.

[a] Categories of modified informed consent: (1) arms and chances: the number of arms in a study, or a participant's chances of receiving the study drug; (2) drugs and/or dosages: the specific drug and/or dosages of a drug that a participant could receive (eg, telling participants they may receive drugs or dosages of drugs that were not actually administered, ie, red herrings); (3) placebo features: the specific drug or dosage used in a study as the comparator or the intent of using those drugs and comparators.

[b] Note that none of the studies in the table assessed expectancy.

[c] All studies labeled randomized had an equal (1:1) distribution between arms, eg, 50% in a 2-arm trial, unless otherwise specified.

[d] Whether a drug was considered an active comparator was dependent on whether any subjective effects would be expected from the dosage of the drug.

[e] Participants completed a "pharmacological class questionnaire" or an "end-of-session questionnaire," which asked participants to rate the similarity of their drug experience to various different drug classes.

[f] Participants were randomly assigned to 3 different dose groups in a 1:1:2 ratio.

standardized implementation a challenge.[43] The 4 criteria described above offer a framework for discussions with individual IRBs, as some psychedelic RCTs likely meet these criteria.

In the psychedelic RCTs that modified informed consent (Table), investigators obscured or withheld information about 1 or more of the following: (1) arms and chances: the number of arms in a study or a participant's chances of receiving the study drug; (2) drugs and/or dosages: the specific drug and/or dosages of a drug that a participant could receive (eg, telling participants they may receive drugs or dosages of drugs that were not actually administered, ie, "red herrings." Standard informed consent requires that the specific dosages to be administered are communicated to participants); (3) placebo features: the specific drug or dosage used in a study as the comparator or the intent of using those drugs and comparators. These modifications were likely considered ethical because they did not increase risks for participants (eg, not knowing one's odds of receiving the active treatment does not pose an immediate health risk).

Can Modifications to Informed Consent Improve Masking in Psychedelic Studies?

Modifications to informed consent have been implemented in psychology studies[28,44,45] and pharmacological experiments in healthy participants,[46] fear conditioning experiments in patients with PTSD,[28,47] the bogus taste test for binge eating disorder,[48] the ad libitum taste test in alcohol drinkers,[49] survey studies in alcohol use disorder,[28,50] an RCT of an SSRI for social anxiety disorder,[51] and an RCT of a method to taper benzodiazepines.[52]

While these studies support the idea that modifications to informed consent can be ethical and might improve masking, these previous studies were not focused on determining if modified informed consent improves masking success per se. Instead, these previous studies used modified informed consent to be able to investigate phenomena that could not be studied without such modifications, eg, measuring the effects of deception on eating or alcohol use or studying the effect of expectancy on responses to SSRIs or a benzodiazepine taper. Thus, no appropriately designed RCTs have investigated the effects of modified informed consent on masking efficacy. Ten psychedelic studies have modified informed consent (Table), but only 5 measured masking efficacy[33,35,36,38,40] (eTable in the Supplement). Interpreting masking efficacy data is complex, as the chance guess rate in a study depends on the number of options on the masking survey (eg, if the survey had 2 options, the chance guess rate is 50%), and guess rates will likely differ between treatment arms (eg, it might be easier for a participant to tell they received a high-dose psychedelic vs a placebo or vice versa). Where available, we have included the surveys used, chance guess rates, and ratios of correct guesses to chance guess rates that can be used to compare between studies in the eTable in the Supplement. Masking efficacy ranged from complete functional unmasking[33] for high-dose psilocybin to partial unmasking for high-dose MDMA.[38] However, given differences in sample characteristics and study designs, these trials are too dissimilar to support strong conclusions about how or if specific modifications to informed consent mediate differences in masking efficacy. Studies specifically designed to test the effects of consent modifications on masking efficacy are needed.

Guardrails to Mitigate the Risks of Modified Informed Consent

Even if modifying informed consent is critical for informative psychedelic trials and can be ethically justified, there are ethical risks to consider. For example, asking participants to decide whether to enroll in a greater than minimal risk RCT equipped with less information compared with standard informed consent (eg, the true odds of receiving the active treatment) could mean that participants consent to a trial that they otherwise would not. We suggest multiple guardrails that may help attenuate this risk. One guardrail is required by current regulatory guidance, while others come from the bioethics literature and may only be appropriate for specific study designs and experimental contexts.

Required by Guidance: Debriefing

As discussed above, debriefing is required by the APA and Belmont guidelines for studies that modify informed consent. Participants can be surveyed at the conclusion of the trial about how they were affected by consent modifications and if they would have participated in the trial had they known this information; these data could be published with trial outcomes. However, the timing must be carefully considered because debriefing before the end of the trial could lead to unmasking of new participants through personal communications or online forums.

For Consideration: Participatory Research

Studies that modify informed consent may benefit from community-based participatory research approaches,[53,54] such as partnering with people with lived experience of the condition being studied[53,54] and their care partners.[55] These individuals can help investigators decide if modifications to informed consent are considered ethical by those most directly affected. While not required, this input may help researchers determine an acceptable level of ethical risk for the patient population in question and which guardrails could be implemented to mitigate this risk. These approaches are already commonly used in studies in which informed consent is not possible to achieve, such as those in emergency settings and in participants with diminished cognitive function.[56]

For Consideration: Participant-Authorized Modifications

Rather than simply including red herrings or omitting information during the informed consent process, investigators can explicitly tell potential participants that information about certain aspects of the study has been intentionally omitted or misdescribed. If individuals receive this information and still opt to proceed, they effectively "authorize" the use of modified informed consent. Participant-authorized modifications increase transparency about the level of uncertainty involved, allowing individuals to avoid enrolling in studies that withhold or misdescribe information if they prefer. For sample consent language for participant-authorized modifications, see the eAppendix in the Supplement.

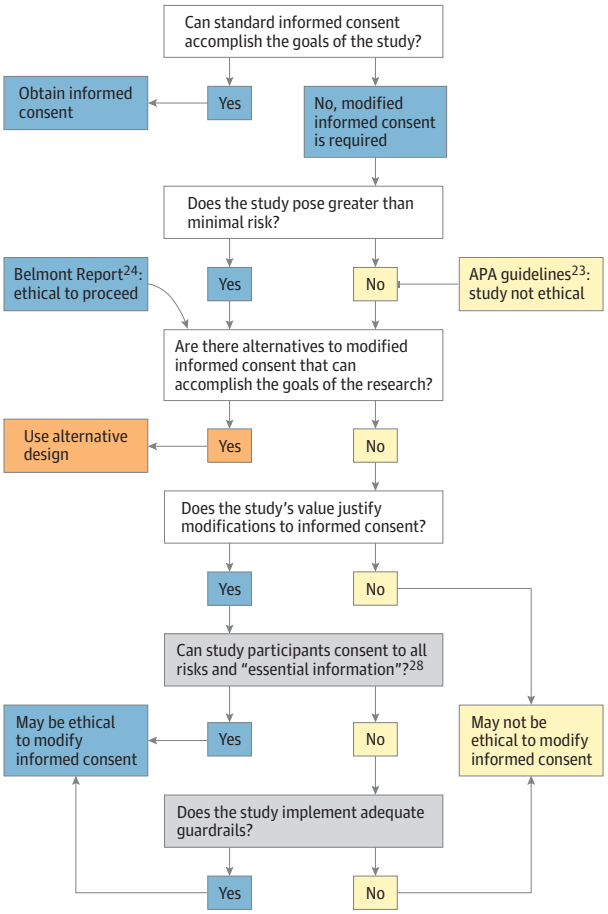
For Consideration: Guaranteed Access to Active Treatment

In optional open-label extension arms or crossover trial designs, participants know they will ultimately receive the active treatment. This could help mitigate the ambiguity that participants must accept in studies that obscure information about the chances of receiving the study drug, possibly making it less challenging to weigh risks and benefits (even relative to 2-arm placebo-controlled RCTs). Importantly, there is disagreement about the ethicality of providing open-label treatments with unknown safety and/or efficacy, such as psychedelics, as this approach clashes with clinical equipoise while offering little knowledge gain (discussion in Taylor et al[57] and Nash[58]).

For Consideration: Measure Expectancy and Masking Efficacy

Measuring baseline treatment expectancy and assessing its relationship with outcomes, considering the expected timing of therapeutic benefits, is an important step for the field. Once more data are available on which measures of expectancy and at which time points they are useful for predicting outcomes, expectancy data could be used to recruit participants who are in equipoise about the efficacy of psychedelic therapy or to balance groups by baseline expectancy, which may help address the effect of expectancy on outcomes. "Double-masked" psychedelic RCTs should also make efforts to mask participant-facing study staff and those conducting data analysis, in addition to participants. Masking success should be measured for participants and staff, ideally immediately after the intervention and at the conclusion of the trial. This timing of assessments can help separate unmasking due to acute subjective experience from unmasking due to clinical improvements. Measuring expectancy and masking success is critical to interpreting study results in general and will help determine whether modifications to

Figure. Decision Tree for Ethical Use of Modified Informed Consent



Decision tree of process to determine whether modifications to informed consent are ethical. White boxes indicate steps included in the American Psychological Association (APA) and Belmont Report guidelines. Gray indicates steps that are not specifically included in regulatory guidelines, or are only partially included, but are discussed in the bioethics literature. Blue indicates that a criterion is satisfied and that it is likely ethical to continue to the next step. Yellow indicates that a step may not be ethical according to at least one guideline. Orange indicates that alternative methods should be tried instead.

informed consent achieve their stated purpose. However, a major challenge is that there is no consensus on best practices to measure expectancy or masking (see the eTable in the Supplement for further discussion). Developing standardized best practices to measure expectancy and masking success is a critical need for the field.

For Consideration: Sharing Consent Language

The specific consent language used across studies is seldom made public, making it difficult to understand the details of any modifications and participants' experiences during the consent process. Publishing this information will allow IRBs, bioethicists, other researchers, and community members to better assess the ethics of consent modifications and contextualize findings. Relevant excerpts from a publicly available consent form from one psychedelic RCT that modified informed consent[40] is included in the eAppendix in the Supplement.

Conclusions and Perspectives

To avoid a crisis of confidence in clinical psychedelic research, we must address functional unmasking. Modifying informed consent may help mitigate this challenge, but there is no universally accepted regulatory guidance for this approach, and it requires careful consideration of ethical risks. Further, no empirical studies have tested if modifying informed consent actually improves masking success. Psychedelic RCTs that modify informed consent may be considered ethical if all essential information is disclosed (especially all significant risks) and adequate guardrails are implemented, given that (1) psychedelics show significant therapeutic promise for multiple neuropsychiatric conditions; (2) additional studies may not yield interpretable data about the efficacy of psychedelic drugs unless masking is improved; and (3) without modified informed consent, we lack strategies to address ineffective masking. We offer a decision tree to assist in navigating regulatory guidance about modified informed consent in the **Figure**.

Each psychedelic RCT involves unique considerations, including the safety and efficacy of the specific intervention, clinical population, risk of masking failure, and strength of participants' expectations. IRBs must carefully evaluate the scientific value of studies that propose to modify informed consent, as generating relevant data can help researchers understand whether modifications in greater than minimal risk psychedelic trials are warranted. In turn, investigators must grapple with and discuss relevant bioethical and regulatory considerations with their IRBs. Perhaps most critical is that the psychedelic research community continues to engage with other researchers, bioethicists, regulatory bodies, payers, and patient communities regarding the use of modified informed consent in psychedelic RCTs. Ongoing discussion of different approaches to improve masking and dissemination of findings regarding masking will ultimately translate into more rigorous and impactful trials in the psychedelic field and beyond.

ARTICLE INFORMATION

Accepted for Publication: October 29, 2024.

Published Online: January 8, 2025. doi:10.1001/jamapsychiatry.2024.4312

Author Contributions: Ms Matvey and Dr Kelley contributed equally as co–first authors.

Conflict of Interest Disclosures: Ms Matvey reported being an employee of MindMed outside the submitted work. Dr Kelley reported support from a Veterans Administration Mental Illness Research, Education, and Clinical Center (MIRECC) Data Science Fellowship in Trauma and PTSD Research. Dr Chiong reported grants from the National Institutes of Health National Institute on Aging (K24AG083117) during the conduct of the study. Dr Woolley reported grants from Filament Health and Usona Institute; nonfinancial support (drug supply program) from Filament Health and Usona Institute; being a Department of Justice expert witness; and being a paid consultant for Magdalena Biosciences, Arcadia Medicine, Reunion Neurosciences, Silo Pharma, Empyrean Neuroscience, Gilgamesh Pharma, Alvarius, and the Alexander Shulgin Research Institute. No other disclosures were reported.

Additional Contributions: We thank the support staff at University of California, San Francisco, and San Francisco Veterans Administration Medical Center, whose tireless work made this and all of our other work possible. We also thank Katy Venable, PhD, Department of Comparative Biomedical Sciences, Louisiana State University, and Jon Cogburn, PhD, Department of Philosophy, Louisiana State University, and our laboratory members at the Translational Psychedelic Research Program, who have helped us think through many of the ideas and perspectives outlined in this article and whose support has been invaluable to this work.

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