A Psychedelic Experience With CDISC

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ABSTRACT

With the interest in Psychedelics ever increasing and the pool of Psychedelic trials rapidly expanding, it is important to understand how the world of Psychedelics and CDISC cross paths. In-depth examples provided by CDISC should provide those working on Psychedelic trials a clear path on how to format and structure the data, in turn reducing any ambiguity. However, it may not always be clear from the CDISC documentation as to what, where and how data is expected to be included. At MAC, through the multitude of Psychedelic trials worked on, we have seen situations where CDISC has been both helpful and potentially frustrating, leaning towards a potential for some improvement. Through this paper we will cover the link between Psychedelic trials and the CDISC standards, identifying pitfalls along the way.

INTRODUCTION

The thought of psychedelic drugs being used to treat poor mental health 20 or even 30 years ago would likely have seemed unbelievable. But the interest has increased exponentially over the past few years. Throughout this paper, we will look at the how psychedelic trials interact with the CDISC documentation, and some general points about the efficacy of a psychedelic trial, and hopefully identify areas of improvement.

TIMELINES OF PSYCHEDELICS

Since the first psychedelic trial of Lysergic Acid Diethylamide, or more commonly known as LSD, back in 1943 [2], the interest of what psychedelics do and how they can positively impact people's health is becoming more important. The number of trials being run on various psychedelics has increased massively over the past few years, as is shown by Figure 1.0. The most common psychedelics being investigated are Psilocybin, 3,4-Methylenedioxymethamphetamine (MDMA), LSD and N,N-Dimethyltryptamine (DMT) [4][5][6][7], with the vast majority being performed on Psylocibin [8]. Due to the nature of psychedelics, the main benefit of their use is in treating mental disorders [9][10]. With conditions linked to depression typically being investigated to see how these psychedelics could improve someone's condition. These depressive conditions can include Major Depressive Disorder (MDD) and Treatment-resistant depression. As of 2021, psychedelic drugs are only legally permitted for psychedelic therapy within clinical trials [11][12].

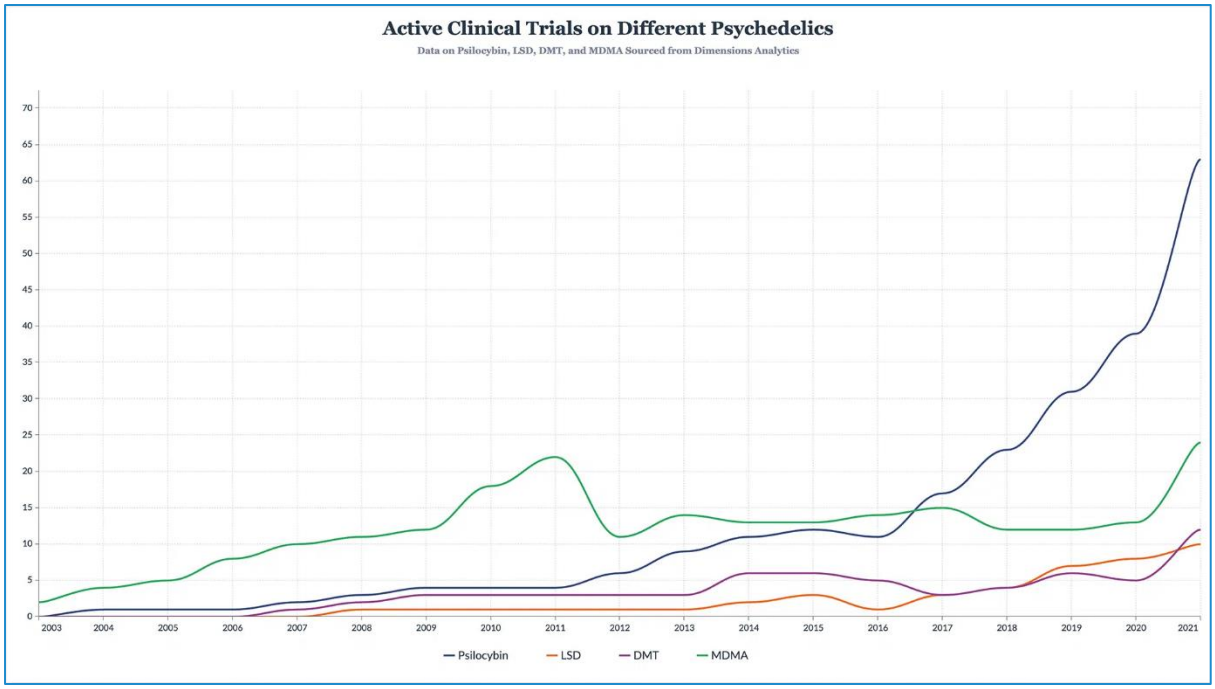


Figure 1. Graph to show the increase in psychedelic trials over the past 20 years. [3]

A compounding factor to why psilocybin is chosen in many trials as the “psychedelic of choice” is due to the minimal risk of toxicity and low potential for dependence or addiction [13]. Many countries, including Portugal, the Netherlands and Canada, have made its use more available to the public, via over-the-counter sales or being made available to people with life-threatening illnesses through compassionate-use regulation [14].

There has been strong evidence of the therapeutic benefits of psychedelics [15]. However, due to legal reasons, such as the Drug Reform Policy released in 2021 [16], public use of psychedelics is not possible until any potential risks and any proposed benefits have been fully investigated. For example, in the UK, there are discussions about legalising Psilocybin, which will inevitably see more clinical trials focused on psychedelics, creating more data around psychedelics, and navigating this vast amount of data is becoming ever challenging. However, CDISC has already made great steps to alleviate exploring and transforming this data by defining robust standards while potentially inadvertently complicating parts at the same time.

HOW DO PSYCHEDELICS WORK?

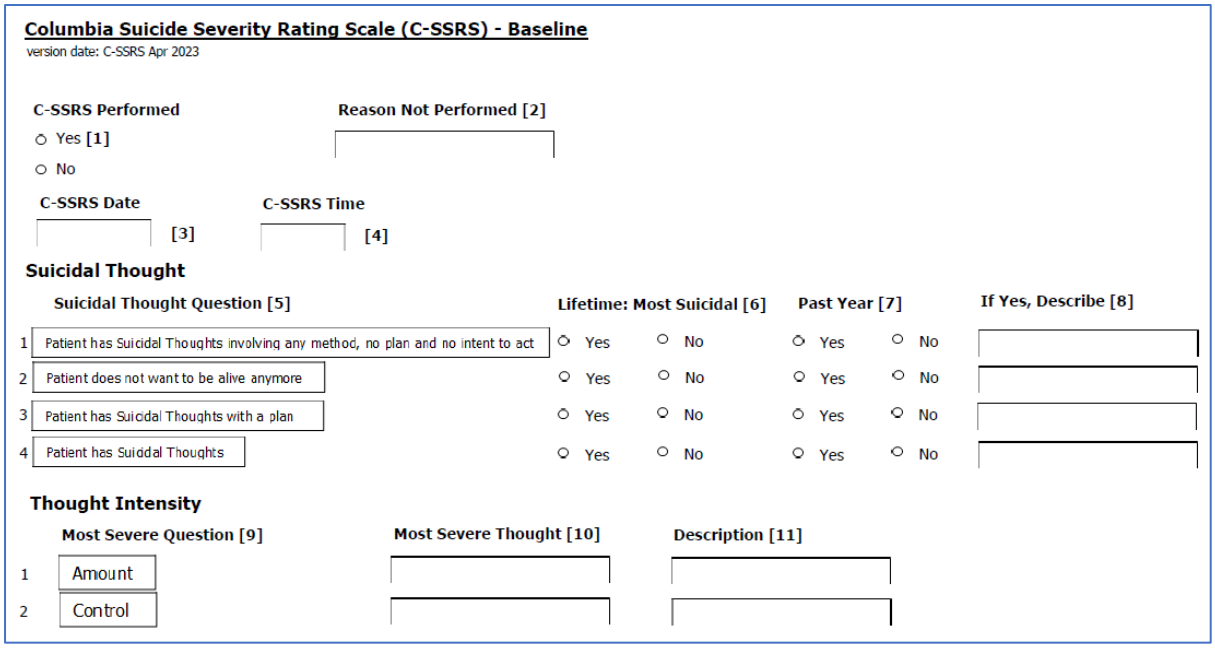
Most psychedelics fall into one of three families of chemical compounds: tryptamines, phenethylamines or lysergamides. They all take action via serotonin 2A receptor agonism [18]. When these compounds interact and bind to serotonin receptors, they modulate the activity of key circuits in the brain involved with sensory perception and cognition [19]. However, the method about how they induce changes in perception and cognition via the 5-HT receptor is still unknown [17]. But a reduction in default mode network activity and increased functional connectivity between regions in the brain may be one of the most relevant pharmacological mechanisms underpinning the psychedelic experience [20]. To put it simply, psychedelics are substances that induce a heightened state of consciousness characterised by a hyperconnected brain state, so that the number of nodes far exceed the number of users in the brain. We know how they interact, so how do we measure this interaction and thus a psychedelics effectiveness? One word – questionnaires.

DATA CAPTURE

As psychedelics are used to treat mental disorders this results in a lot of questionnaires being used. Figure 2 below shows the list of questionnaires seen in a trial we recently undertook here at MAC, as you can see there are a fair few.

Figure 2. A list of Questionnaires on a Psychedelic Trial. Due to copyright, we discuss the general use of some of these questionnaires listed, we have used adjusted questionnaires in some instances, but the idea is still the same.

As you can see from Figure 2, the range of questionnaires to be completed on a study is vast, but this varies between studies. CDISC's Study Data Tabulation Model (SDTM) and corresponding Implementation Guide (IG) defines a couple of domains for capturing this type of data, most commonly Questionnaire (SDTM.QS) and the Disease Response and Clin Classification (SDTM.RS) domains. Which when used in any study are never particularly small.



Columbia Suicide Severity Rating Scale (C-SSRS) - Baseline

version date: C-SSRS Apr 2023

C-SSRS Performed

○ Yes [1]

○ No

Reason Not Performed [2]

C-SSRS Date [3]

C-SSRS Time [4]

Suicidal Thought

	Suicidal Thought Question [5]	Lifetime: Most Suicidal [6]		Past Year [7]		If Yes, Describe [8]
1	Patient has Suicidal Thoughts involving any method, no plan and no intent to act	○ Yes	○ No	○ Yes	○ No	
2	Patient does not want to be alive anymore	○ Yes	○ No	○ Yes	○ No	
3	Patient has Suicidal Thoughts with a plan	○ Yes	○ No	○ Yes	○ No	
4	Patient has Suiddal Thoughts	○ Yes	○ No	○ Yes	○ No	

Thought Intensity

	Most Severe Question [9]	Most Severe Thought [10]	Description [11]
1	Amount		
2	Control		

Figure 3. An example Questionnaire CRF page from a Psychedelic Trial.

Above is an example of a typical Case Report Form (CRF) seen on a trial. The amount of information collected sometimes makes it hard to map out all information collected correctly. The CDISC IG provides useful “tips” for mapping the data correctly and consistently between each questionnaire, however aside from the IG, there are the Controlled Terminology (CT) dictionaries produced by the National Cancer Institute in partnership with CDISC which also aid this transformation.

These CT dictionaries contain terms for some of the more commonly used questionnaire pages, like Columbia Suicide Severity Rating Scale (C-SSRS) but therein lies the first issue, not all are defined in the CT documents, opening the door for free reign. The next issue is somewhat a little silly, we are limited to storing questionnaire questions to 40 characters or less, the reason is trivial, but we will not go into why we have this restriction, all I am going to say is the format we send our datasets to the regulators is the SAS® transport version 5.0 which was created in 1989! Anyway, due to the length of questions typically being asked usually exceeding this 40-character limit we are left with a jumbled mess sometimes, let me explain.

CONTROLLED TERMINOLOGY

A commonly seen questionnaire is the Columbia Suicide Severity Rating Scale (C-SSRS), specifically the Baseline/Screening questionnaire. CDISC defines the questions themselves as labels and codes, with the labels defined under the code list named CSS04TN and the coded terms under the code list CSS04TC, which is shown in figure 4 below.

CSS04TC (Columbia-Suicide Severity Rating Scale Baseline/Screening Version Questionnaire Test Code)

NCI Code: C106661, Codelist extensible: No

C106661	CSS04TC			
NCI Code	**CDISC Submission Value**	**CDISC Synonym**	**CDISC Definition**	**NCI Preferred Term**
C106707	CSS0401A	CSS04-Wish to be Dead-Life	Columbia-Suicide Severity Rating Scale Baseline/Screening Version - Have you wished you were dead or wished you could go to sleep and not wake up? (Lifetime).	C-SSRS Baseline/Screening Version - Wish to be Dead (Lifetime)
C106708	CSS0401B	CSS04-Wish to be Dead-P_M	Columbia-Suicide Severity Rating Scale Baseline/Screening Version - Have you wished you were dead or wished you could go to sleep and not wake up? (Past _ Months).	C-SSRS Baseline/Screening Version - Wish to be Dead (Past X Months)
C106709	CSS0401C	CSS04-Wish to be Dead, Describe	Columbia-Suicide Severity Rating Scale Baseline/Screening Version - Description of wishing to be dead.	C-SSRS Baseline/Screening Version - Description of Wish to be Dead
C106710	CSS0402A	CSS04-Non-Spec Suicid	Columbia-Suicide Severity Rating Scale	C-SSRS

Figure 4. Coded code list for the Columbia Suicide Severity Rating Scale (C-SSRS).

As you can see, due to this 40-character limit the values are restricted and shortened when compared with the question asked on the CRF, and this is true with most questionnaire code lists. Notice the addition of the prefix “CSS04-“ which reduces the limit to 34 characters, it is worth noting this prefix is included to account for uniqueness due to there being multiple different versions of the C-SSRS questionnaires, i.e., the original one, one for baseline only, one for since last visit, etc.

As an example, on the official C-SSRS questionnaire, the questions are quite descriptive of what is being asked, for example, one of the questions from the CRF in Figure 3 states, “Patient has Suicidal Thoughts involving any method, not plan and no intent to act” which covers both a persons’ “lifetime” and “over the last 12 months”. Now following the CDISC SDTM standard, when we map this into the SDTM.QS domain this question will be split into two questions, firstly “CSS04-Idea, No Intent, No Plan-Life” for the lifetime part and secondly “CSS04-Idea, No Intent, No Plan-P12M” for the Past 12 Months part. This abbreviated text does not explain the original question particularly well. Similar things happen in other cases, with words being truncated as a way of conforming to this ridiculous character limit, such as “Has subject engaged in Non-Suicidal Self-Injurious Behaviour? If Yes, Describe” being shortened to “CSS04-Non-suicidal Self-injur Behav-Desc”. If the reader is unfamiliar with the study and information being collected, this truncation of words will inevitably cause some confusion.

This then leads to our own question of “should we follow the same naming process for code lists not defined by CDISC to ensure consistency?” or with the 40-character limit applied “Follow naming proc for CL not pre-defined for cons?”. For example, here is another questionnaire to be included on the same study, the Mental Wellbeing State or MWS for short. This questionnaire is not defined in the current version of the CT dictionaries, but the questions are all very long, and a subjects’ results towards the higher end of the range will show a subject is struggling with their mental health, as opposed to those with lower values showing someone who may be in a better position mentally.

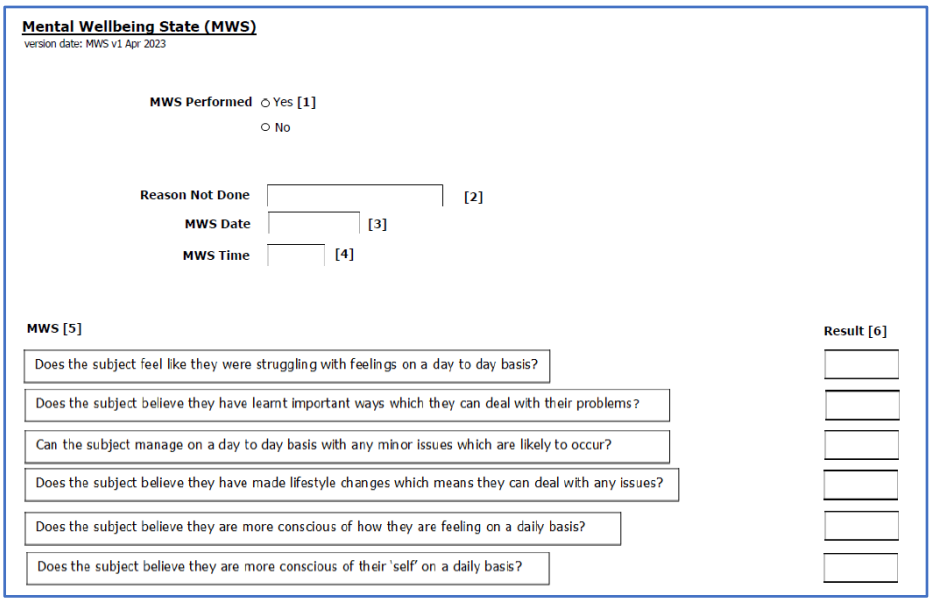


Figure 5. Example of a Questionnaire CRF page which has questions with long text.

Let us employ the same prefix rule, with the text “MWSxx-”, this limits us to 34 characters to fit the text. The first question “Does the subject feel like they were struggling with feelings on a day-to-day basis?” Can be set to “MWS01-Struggling on a Daily Basis” which gives us a gist of what the question is asking but it is not the full question.

CDISC QUESTIONNAIRES, RATINGS AND SCALES (QRS)

The CDISC Questionnaire, Ratings and Scales or QRS team are a group of volunteers who investigate how the series of questions, tasks or assessments used to provide a qualitative or quantitative assessment of a clinical concept or task-based observation is being mapped. Anyone can suggest a new QRS Supplement by filling in a QRS Supplemental Request Form, which can be found

on the CDISC website [1]. This request process involves creating the following documents: QRS Standard Request Form, QRS Public Domain Copyright Verification Document, CDISC Copyright Letter, QRS Supplement Template (Based on appropriate domains, such as QS, FT, and RS), QRS Terminology Spreadsheet Example, QRS Naming Rules, QRS Supplement QC Checklist v2. [1]

As seen, it is not always easy to know where to map a particular questionnaire to a specific SDTM domain, usually it will be either the Questionnaire (QS) domain or the Disease Response (RS) domain so let us look at another example, where this distinction is less clear.

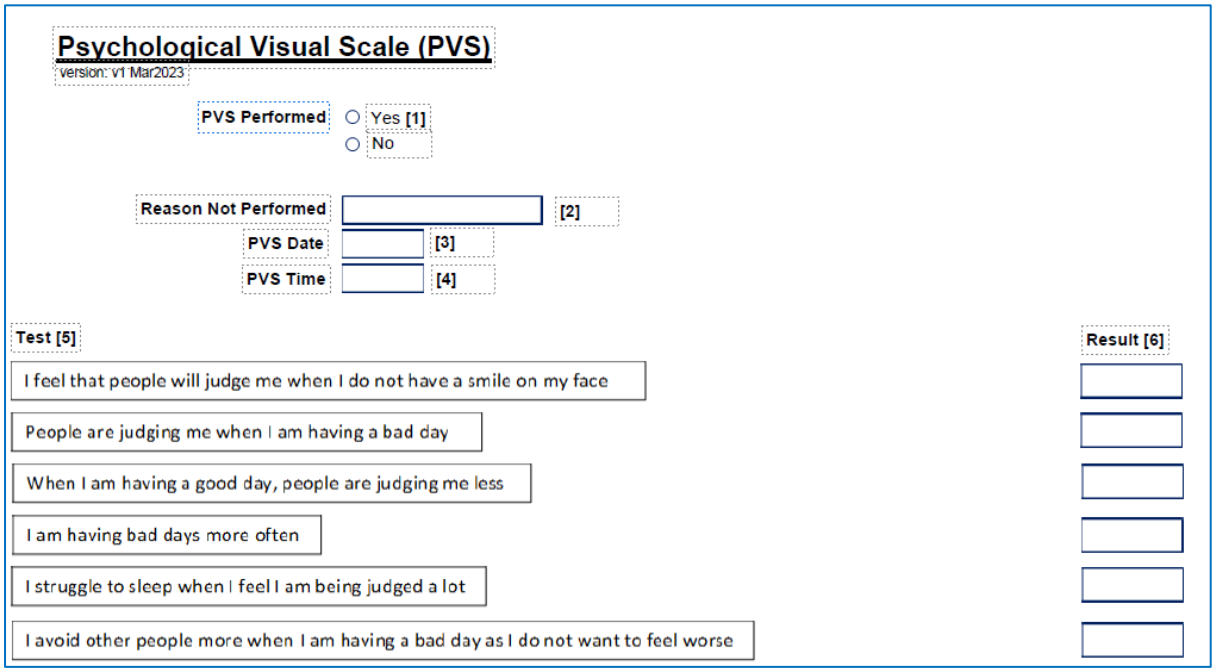


Figure 6. A CRF page showing part of the Psychological Visual Scale (PVS) questionnaire.

The information collected here seems like it could fit in either domain (QS or RS). Due to this possibility and how much of a grey area it can be, we would turn to the CDISC QRS team. The QRS standards cover several different questionnaires, of course this does not cover all cases but does deal with a good portion of them. As shown in Figure 7 below the website provides guidance which includes resources to aid in the production of both Tabulation Datasets (including SDTM) and the Analysis Datasets (such as CDISC ADaM). Additionally, and specifically with the Tabulation datasets there are further resources showing an example CRF, illustrating how particular questions from a specific questionnaire are typically displayed. CDISC even includes a supplemental domain (SUPP--) examples, when applicable, for those fields which may not be captured by the parent domain, i.e., QS or RS. Having further examples on the QRS page would be a massive help to psychedelic trials.

Figure 7. A screenshot of the CDISC QRS supplemental for the 10-Meter Walk/Run Questionnaire.

It would be a great aid to the programming community for a psychedelic trial therapeutic area user guide (TAUG), and maybe a call to arms for people to submit their questionnaires to the QRS team, to strengthen this library of resources. In an ideal world, dropping this 40-character limit would likely improve understanding of the code lists.

QUESTIONNAIRE FATIGUE?

Due to this excessive amount of questions being asked of the participants during a psychedelic trial, is it possible that the responses are being skewed one way due to questionnaire fatigue? Psychedelic fatigue could cast doubt on the outcome of these psychedelic trials, maybe due to the chance that participants are not answering truthfully but are potentially answering each questionnaire quickly with very little thought. We have all done those internal company questionnaires, which go on and on, now this is just a hunch and clearly speculation. In fact, regarding company questionnaires, we recently removed the middle option in our company 5-point questionnaire, as when everyone answers “Neither Agree nor Disagree” this tells us nothing.

Alternatively, how can you truly measure cognition while on these psychedelic experiences, when they could be answering the questions randomly due to them wanting to enjoy the experience, with little outside interference? Again, just a thought. Most questions are asked once, but there are instances where the same questions are asked on multiple occasions, at different timepoints during the psychedelic experience, which can mean there are hundreds of questions asked per subject on a single study.

As an example, recently on a trial here at MAC there was the questionnaire titled “Intensity of Psychedelic Experience Questionnaire” or IPE for short, which was administered to the Participant at 20-minute intervals post-dose until the effects of the psychedelic had waned. This can lead to a large chunk of time being taken to simply answer all the questions asked, whether by the investigator or the participant. There is also the possibility that the participant may not be aware of questions being asked if the psychedelic experience is quite strong. Now I am no expert, but is there any way around the risk of questionnaire fatigue? Due to the nature of psychedelic trials, currently it is not possible to not include this level of questionnaires. So, the assumption that participants are answering the questions to the best of their knowledge must be assumed, but we do need better mechanisms.

HIGH DROPOUT RATE

As may be expected on a trial containing drugs which are prohibited for public use, there is the risk of participants dropping out after completing their screening visit. For example, I have seen a study which had 250 participants enter the study, but only 48 made it to the point of taking the study medication, resulting in a retention rate of just 20%. This low percentage is not unfamiliar and likely due to multiple reasons which the participants may not have thought would be a factor, and high drop-out rate or screen failure rates is nothing new.

The industry interest and publicity of these psychedelic trials is a great advantage, but if the retainment rate is as above, it results in the overall trial timelines being extended well beyond the planned study duration. Is this high dropout rate just a onetime occurrence or is it down to participants hoping to get the opportunity to experience their first psychedelic experience without considering the full impact of the trial? This is not a fact, just a programmer’s opinion, food for thought even. Whatever the case, high dropout rate and longer studies result in one thing, adding unnecessary costs [8].

CONCLUSION

The prevalence of psychedelic trials is exponentially growing year on year, with a quick search on the government portal for the word “psychedelic” returning 625 studies currently ongoing and or recruiting [22]. This is no surprise with mental health disorders currently rising [21]. With recent developments in CDISC we are likely not far from a psychedelic specific therapeutic area user guide (TAUG) in the coming months as we see more and more trials move to completion. Resulting in more information around the lesser-known questionnaires thus aiding the mapping from raw data to the CDISC standards. There is clearly a need to look at questionnaire fatigue and high dropout rates in psychedelic studies and I would be curious to see what some exploratory analysis on completed psychedelic trials would show.

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