Medical Anthropology Quarterly

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# MDMA Is Not Ecstasy: The Production of Pharmaceutical Safety through Documents in Clinical Trials

*Nonprofit efforts to develop ±3,4-methylenedioxymethamphetamine (MDMA)—better known as the street drug Ecstasy—as a prescription pharmaceutical provide the opportunity to examine recent theorizations of pharmaceuticals as fluid objects transformed in new informational and material environments. Drawing from ethnographic research, this article interrogates MDMA researchers' own distinction between MDMA and the street drug Ecstasy. While researchers maintain that pure MDMA is distinct from Ecstasy, this article argues that the difference between the two hangs not on a distinction in substance, but on a distinction in safety that must be produced through the trial. This article tracks the production of safety through the inter-connected work of clinical documents, which manage both which bodies are allowed to absorb the drug and which bodily events count as effects. MDMA's safety emerges from the careful management of relations through these documentary practices.* [pharmaceuticals, clinical trials, knowledge production, science studies, psychedelics]

In 2001, the Food and Drug Administration (FDA) approved an unusual protocol: a pilot study testing the safety and efficacy of ±3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in subjects with chronic posttraumatic stress disorder (PTSD). The study was unusual for several reasons. First, the sponsor was neither a pharmaceutical company nor a research university, but a small nonprofit organization, the Multidisciplinary Association for Psychedelic Studies (MAPS). Second, MDMA was then, and remains now, a Schedule I substance that is more commonly referred to as Ecstasy—a recreational drug known for producing powerful feelings of empathy and trust. By definition, Schedule I includes substances with a high probability for abuse and no therapeutic application. MAPS maintained that MDMA—contrary to the parameters of Schedule I—could be administered *safely* in a controlled environment and that the drug had a therapeutic application, albeit one that had not yet been formally studied in rigorously conducted clinical trials. They argued that MDMA's therapeutic effects were not absent. Rather, they were *not yet* studied.

*MEDICAL ANTHROPOLOGY QUARTERLY*, Vol. 35, Issue 1, pp. 5–24, ISSN 0745-5194, online ISSN 1548-1387.  DOI: 10.1111/maq.12548

While MDMA is best known as a recreational drug, the substance is in fact an old product of the pharmaceutical industry that was originally synthesized and patented by Merck pharmaceuticals at the beginning of the 20th century, though the company never developed an application for the drug (Freudenmann et al. 2006). However, MDMA's particular molecular structure—part amphetamine ring and part mescaline ring—made it of interest to psychotherapists experimenting with psychedelic substances in California in the 1970s (Stolaroff 2004). The psychotherapeutic use of psychedelics can be traced back to the middle of the 20th century when psychiatrists in both private and institutional settings developed techniques for integrating these unusual substances into psychotherapy. This emergent style of clinical reasoning combined biological theories of mental illness, Jungian psychology, and spirituality (Dyck 2008). In the 1970s and early 1980s, MDMA was not yet a scheduled substance and was thus a legal therapeutic alternative to LSD, psilocybin, and other psychedelics, which had been recently criminalized. MDMA was praised for increasing trust, enabling communication and self-understanding, and increasing self-confidence and self-acceptance (Greer and Tolbert 1986; Stolaroff 2004; Wolfson 1986).

The approval of the first MDMA study protocol in 2001 was the result of 15 years of work by MAPS. In 1986, shortly after the Drug Enforcement Agency (DEA) scheduled MDMA, the recently founded MAPS organization opened a Drug Master File (DMF) for MDMA with the FDA. While the DEA may have been able to schedule MDMA, the FDA can still evaluate the therapeutic potential of a substance and make a recommendation to reschedule the drug if there is a viable therapeutic application. Over the next three decades, MAPS has worked though regulatory channels in the United States and abroad to develop a clinical development program centered around MDMA-assisted therapy for PTSD—strategically chosen because of the weakness of psychopharmaceutical comparators and from anecdotal reports that the drug had helped subjects overcome defenses from traumatic events (Greer and Tolbert 1986; Wolfson 1986).

In 2010, I joined MAPS' clinical team as an intern as part of my doctoral fieldwork on the redevelopment of MDMA as a prescription pharmaceutical. At the time, MAPS' offices were located inside a small 1940s 'cottage-turned-office space on a busy thoroughfare in Santa Cruz, California. I sat down with the lead clinical research associate, Beth, who supervised interns like myself, to explain my project and my interests. I came to MAPS' program having already worked on ethnographic studies of drug use in the rave and club scene and as I began to explain my project, I called the drug Ecstasy out of habit.

Beth quickly interjected, "We aren't studying Ecstasy. We are studying MDMA."

"Sorry, MDMA," I apologized.

"It is okay," she said. "I have to correct people all the time. We are studying MDMA, which is not the same thing as Ecstasy."

Beth's distinction caught me off guard. MDMA and Ecstasy have been socially, bureaucratically, and academically linked for decades.[1] Ecstasy is ostensibly the street name given to the chemical substance MDMA. And MDMA is the defining chemical element of Ecstasy. Media accounts trace the use of Ecstasy as a name for MDMA back to the Texas club scene in the early 1980s (Obenhouse 2004). In fact, the DEA website lists both MDMA and Ecstasy as street names for the

controlled substance ±3,4-methylenedioxymethamphetamine (Drug and Chemical Evaluation Section 2013). The academic literature negotiates the overlapping definitions through parenthetical references linking the two terms, such as MDMA ("Ecstasy") or Ecstasy (MDMA). To make a pharmaceutical parallel, it was almost as if they were claiming that fluoxetine was not the same thing as Prozac.

MAPS' website clarifies Beth's distinction:

> MDMA is not the same as "Ecstasy" or "molly." Substances sold on the street under these names may contain MDMA, but frequently also contain unknown and/or dangerous adulterants. In laboratory studies, pure MDMA has been proven sufficiently safe for human consumption when taken a limited number of times in moderate doses (MDMA-Assisted Psychotherapy 2018).

MAPS' explanation presents two different rationales for the distinction between Ecstasy and MDMA. The first rationale locates the difference through substance: the chemical purity of MDMA is opposed to the uncertain chemical multiplicity of Ecstasy. However, there is also a second rationale at work in the quotation, which invokes safety to distinguish the two substances. Pure MDMA, unlike potentially contaminated Ecstasy, has been proven *safe in controlled laboratory settings*. Following a classic move by science and technology studies scholars, I approach MAPS' claim as a black box that must be empirically pried open. I argue that purity, while important, is not enough on its own to secure a claim to the difference between MDMA and Ecstasy. The safety of the substance must first be developed to make the difference in purity matter. Drawing from ethnographic fieldwork with MAPS clinical trial researchers, I follow the cultivation of MDMA's *safety* in what I call the *documentary apparatus* of the clinical trial. In the following sections, I call attention to the production of clinical documents as a key site for the production of clinical evidence of safety. Documents manage both which bodies are allowed to absorb the drug and which bodily events count as effects. MDMA's safety emerges from the careful management of relations through these documentary practices.

This argument draws from recent scholarship on generic pharmaceuticals, which has argued that the identity of chemical substances is not quite as self-evident as we might think. Scholars have drawn attention to the ways that distinctions are made between seemingly identical substances. In the realm of generic or copied pharmaceuticals not only is fluoxetine sometimes different from Prozac, but even different generic versions of fluoxetine may be distinguished from one and other (Hayden 2012; Sanabria and Hardon 2017). This gives way, as Cori Hayden has argued, to a proliferation of generics that are the same but different. In parallel, I argue that MAPS' move to disarticulate MDMA and Ecstasy makes use of this same chemo–pharmaceutical possibility for producing things that are the same but different. In this case, producing MDMA's difference from Ecstasy requires demonstrating its safety.

Concerns around MDMA (Ecstasy)'s safety have long shadowed MAPS efforts to develop a clinical trial program. While MDMA was scheduled in the 1980s, it wasn't until the late 1990s that use of MDMA (Ecstasy) became widespread in the United States—partly through the drug's association with rave parties (Hunt et al.

2010). MDMA (Ecstasy)'s rapid rise in popularity was accompanied by a social panic around the dangers of a relatively unknown drug (Rosenbaum 2002). As I will discuss further, debates around MDMA (Ecstasy)'s safety coalesced around two distinct time scales: the short-term dangers of hyperthermia (overheating) and hyponatremia (water intoxication), and the long-term possibility of neurological damage. Moving forward with MAPS clinical development program has required countering both of these sets of concerns.

This article proceeds from two ethnographic insights into the complexity of the collection of safety data. First, safety is twice baked into the clinical trial—interwoven in the very practices and aims of clinical research. The very same documentary procedures needed to ensure the safety of the participants are also intertwined with the creation of data on the safety of the drug. Second, safety data must both account for known and unknown effects. Thus, documents needed to produce data that countered the specific risks about MDMA (Ecstasy), as well as a detailed assessment of *possible* effects of MDMA in the clinical setting. Neither of these insights is meant as an ethical critiques of these clinical trials. (Though a wide scholarship has called attention to the way that risk is unevenly socially distributed in clinical trials more generally [Abadie 2010; Craddock 2004; Fisher 2009; Jain 2010; Petryna 2009; Saethre and Stadler 2013].) Here, I am speaking to both the broader logic of safety data is clinical research itself, and the specific burden this logic places on producing safety in the MDMA trials.

Drawing from two years of ethnographic fieldwork with MAPS' clinical trial team, this article focuses on the production of MDMA's safety within the *documentary apparatus* of the clinical trial. Recent anthropological scholarship has called attention to the fluidity and leakiness of pharmaceuticals and their corresponding potential for reconfiguration (Sanabria and Hardon 2017). I argue that documents—often looked at, rather than through, in ethnographic research (Hull 2012)—are used to manage the leakiness of the pharmaceutical and thereby the identity of the pharmaceutical under investigation. Clinical research documents are a quite literal inscription device through which the materiality of MDMA becomes data (Latour and Woolgar 1986). However, documents must inscribe more than data. Documents must also inscribe the events of trial itself: the very practices and actions of the researchers, which may be scrutinized down the line in an audit. In the following sections, I ethnographically trace how documents inscribe safety as both a set of research practices and data on MDMA's effects. In doing so, they produce more than evidence of safety; they produce MDMA as a distinct substance.

## Pharmaceutical Associations

The anthropology of pharmaceuticals emerged in the late 1980s and early 1990s through an engagement with the spread of Western pharmaceuticals in the Third World (van der Geest and Whyte 1991). Seminal scholarship drew attention to pharmaceuticals as the "synthesized, manufactured, and commercially distributed therapeutic substances that constitute the hard core of biomedicine" (van der Geest et al. 1996, 154). In this new wave of scholarship, the pharmaceutical was the material instantiation of the intersection of capitalism and biomedicine. Both the overabundance and contested absence of pharmaceuticals enabled discussions of

the contradictions and inequities enabled by the distribution of health via capitalism. The pharmaceutical-as-the-hardcore-of-biomedicine frame created a space for ethnographic discussions of pharmaceuticals as a critical node in globalization (Kleinman and Petryna 2006), citizenship (Biehl 2004; Ecks 2005; Nguyen 2005; Persson et al. 2016), the pharmaceuticalization of health (Biehl 2013; Whitmarsh 2008), and new modes of selfhood (Jenkins 2011).

However, the pharmaceutical-as-the-hardcore-of-biomedicine has a critical lacuna. As scholars have pointed out, the focus on the materiality of pharmaceuticals has ignored the fact that their efficacy is premised on their dissolution (Sanabria 2016). As Emilia Sanabria has pointed out using the language of Tim Ingold, pharmaceuticals are "leaky" things that take effect only through being absorbed into the body (Sanabria 2016). The language of "leakiness" allows Sanabria to avoid discussions of agency and to instead focus on the relation of the substance to a living body that must absorb it for it to take effect. This theme is further developed in Anita Hardon and Emilia Sanabria's recent review of the anthropology of pharmaceuticals literature, where they argue that contemporary scholars—inflected by science and technology studies—are shifting away from an object-centered approach to the pharmaceutical and toward a "process-centered approach that examines the articulations, dearticulations and rearticulations of pharma-matter" (Sanabria and Hardon 2017, 119) Again following Tim Ingold in his concept of "matter-flow," Hardon and Sanabria highlight ethnographic inquiries into the process through which drugs are *rendered efficacious*. In their framing, pharmaceutical effects are neither stable nor distinct from social processes, but are, in fact, a key site for ethnographic inquiry: as when clinical trials attempt to indefinitely extend the pharmaceutical management of risk for chronic disease (Dumit 2012), or when the buying, repackaging, and reselling of generic pharmaceuticals leads to antimicrobial resistance through the consumption of suboptimal doses (Peterson 2014). In both of these cases, pharmaceutical effects have the potential to be continually reconfigured.

In an intertwined conversation, the ethnographic study of generic or copied pharmaceutical markets has called attention to the complexity of chemical identity. Generic pharmaceuticals are a recent category—an artifact of the lifecycle of the patented pharmaceutical—which depends not on substances being identical but sufficiently similar (Greene 2014). However, as Cori Hayden has argued, the generic is not simply the outside of the patented pharmaceutical, but is itself a surprisingly diverse and *specific* category (Hayden 2007). While *a* generic may contain the same amount of a particular substance as *a* branded pharmaceutical, generic *versions* of a pharmaceutical product may differ in color, shape, size, and fillers. And, because the method of manufacture can change how the body absorbs a substance, pharmaceuticals are further distinguished by regulatory agencies through evaluations of bioequivalence. In Hayden's ethnographic work on Mexican pharmaceutical markets, she argues that bioequivalence testing leads to distinctions in quality that have become "a technical–political tool for differentiating generics from themselves and thus, as ever, from their patented counterparts" (Hayden 2007, 481).

For Hayden, the proliferation of sameness-with-difference in pharmaceutical markets challenges analytical and metaphorical framings of chemical substances as reductive. While Hardon and Sanabria focus on how pharmaceuticals are rendered

efficacious, Hayden invokes philosophical debates on chemical identity to highlight the rich complexity of the chemical form prior to, or perhaps, apart from its dissolution. Drawing from chemist Roald Hoffman's treatise *The Same and Not the Same* (1995), which argues that "chemicals are different versions of themselves" (Hayden 2012, 278), Hayden points out that not only do chemists themselves pay close attention to minute variations in chemical structures—for example, two molecules with the same atomic makeup can have different geometries—but also, and more importantly, the discipline of chemistry is attentive to how chemicals vary precisely through their associations, or relations, with their environment.

These conversations are, in fact, approaching two related but distinct problems, both of which are critical for understanding the disarticulation of MDMA and Ecstasy. While Hayden's work on generic pharmaceuticals points us to the complexity of pharmaceutical similarity and difference and its relation to identity, Sanabria and Hardon's discussion points ethnographers toward investigating the processes through which pharmaceutical efficacy is apprehended. In the case of MDMA's relationship to Ecstasy, both discussions are significant. Rendering MDMA distinct from Ecstasy—when MDMA is ostensibly the defining element of Ecstasy—requires the production of a new set of effects. Here, effects fall not under the sign of therapeutic efficacy but of safety.

This discussion points to a central paradox in the sociality of the chemical within contemporary regulatory regimes. Regulatory regimes apprehend pharmaceuticals precisely through notions of stability, purity, and identity. And yet, the fluidity of the pharmaceutical effects and identities is a driver of the both pharmaceutical markets and chemical research and development. The ability of pharmaceutical substance to take on new effects through new associations allows for the development of new applications and markets—as when the antidepressant Prozac was redeveloped, repackaged, and remarketed as Sarafem, a treatment for premenstrual dysphoric disorder (Greenslit 2005). Thus, our analytical languages and ethnographic questions must attend to both the fluidity and leakiness of the pharmaceutical and to the techniques that transform leaky or fluid things into solid pharmaceuticals. In what follows, I ethnographically trace the work of documents in managing the relations between bodies, chemicals, events, and effects, such that MDMA can emerge as a distinct substance. But first, I pause to examine the development of the narrative of MDMA (Ecstasy) as a dangerous drug.

## Anxiety over MDMA (Ecstasy)

Public concerns around MDMA (Ecstasy)'s safety date back to the late 1990s, when the precipitous rise in MDMA (Ecstasy)'s popularity in the United States drew a corresponding spike in media accounts discussing the dangers of the new "designer drug" (Rosenbaum 2002). Several highly publicized deaths from "fake ecstasy," as well as a study claiming that MDMA (Ecstasy) use caused neural damage (McCann et al. 1998), led to a series of public health campaigns, an increase in government-funded research, and increased regulation to combat its use. The leading neuroscience researcher on MDMA (Ecstasy), George Ricaurte, maintained that even one recreational dose of MDMA (Ecstasy) could be neurotoxic and warned that neuropsychiatric problems would emerge as users aged (Morris 1998).

However, the public health impact of MDMA (Ecstasy) use during this time was quite small. While the number of Emergency Department (ED) mentions of MDMA (Ecstasy) increased by 58% from 1999 to 2000, the overall number of mentions was small, only 4,511 out of 1,100,539 total drug mentions and 601,776 drug-related ED episodes. (By contrast, the four drugs mentioned most frequently in ED reports in 2000 were alcohol-in-combination (204,524 mentions), cocaine (174,896), heroin/morphine (97,287), and marijuana/hashish (96,446) (Year-end 2000 Emergency Department Data from the Drug Abuse Warning Network 2001.) However, the emergent narrative of MDMA (Ecstasy)'s potential dangers has continued to shape MAPS efforts to conduct clinical trials on the drug's therapeutic benefits.

Discussions of MDMA (Ecstasy)'s short-term risks were intertwined with its presumed use at raves—all-night dance parties set to electronic dance music. At raves, where users danced for hours in sometimes poorly venerated spaces, MDMA (Ecstasy) could lead to hospitalization or death from hyperthermia (overheating) or hyponatremia (water intoxication). While the hospitalizations had complex causes—including adulterants in the pills and unsafe dance settings—they still fueled a wave of local, state, and federal regulation aimed at curtailing use of the drug by curtailing the rave scene itself (Moore and Valverde 2000; Rosenbaum 2002).

At the same time as concerns were raised about these short-term risks, a series of studies claimed to find serotonergenic damage from MDMA (Ecstasy) use in both animals and PET scans of recreational drug users (McCann et al. 2000; McCann et al. 1994; McCann et al. 1998; Ricaurte et al. 2000; Ricaurte et al. 1988). Critics of the animal studies argued that the 'interspecies scaling model' failed to take into account interspecies differences in drug metabolism and pharmoketics (Grob 2000; Vollenweider et al. 2001), while critics of the PET scan studies pointed to both specific methodological failings, such as the lack of data on the retest variability for their technique (Kish 2002), as well as larger critiques of the implications of the findings. Did changes to 5-HT receptors correlate with behavior changes? Were these changes irreversible or short term? One point made repeatedly was that changes to the brain were not necessarily equivalent with brain damage or neurotoxicity. Rather, changes to the brain might be a sign of productive neuroplasticity—a theory supported by recent research (Grob et al. 1992; Holland 2001; Ly et al. 2018; Nardou et al. 2019). This point was underscored by critics of who drew attention to the fact that the MDMDA (Ecstasy) users in the study had no psychiatric problems (Jansen and Rorrest 1999). Lastly, critics questioned how to empirically separate MDMA (Ecstasy)'s neurological effects from other drugs users consumed. Most drug users engage in poly-drug use, making it difficult to establish a causal connection between a single drug and neurobiological changes (Gouzoulis-Mayfrank and Daumann 2006; Parrott et al. 2001). Dr. Charles Grob, a therapist who has since worked on the clinical studies of psilocybin, wrote, "Indeed, 'ecstasy use' may be turning into a catchword for a collection of variables that includes the infusion of many drugs into a stressful lifestyle, rather than a characteristic defined by ecstasy use per se" (2000, 575).

During the late 1990s, those trying to support clinical studies argued that the therapeutic use of the drug was safer than the recreational use (Grob 2000; Holland 1999; Vollenweider et al. 1999). Those in favor of research with MDMA in clinical settings argued that not only was the dosing used in therapeutic settings much

smaller and less frequent than what was reported in recreational use, but also that the setting itself mitigated some of MDMA (Ecstasy)'s risks. In contrast to the recreational use of MDMA (Ecstasy) at raves, where users risked overheating while dancing for extended periods of time in poorly ventilated areas, defendants of MDMA-assisted therapy argued that the controlled therapeutic setting, where subject's body temperature could be monitored and proper fluids administered, lowered the risk of both overheating as well as the potential neurotoxicity of MDMA (Ecstasy), which could be tied to body heat (Doblin 2002; Grob 2000; Malberg and Seiden 1998).

The debates around MDMA (Ecstasy)'s safety and neurotoxicity peaked in 2002, when *Science* published a study from Ricaurte's laboratory with the unprecedented finding of dopaminergic neurotoxicity in non-human primates (Ricaurte et al. 2002). Not only was this the first time that damage to the dopamine system had been found, but one of the five squirrel monkeys died, which immediately raised questions about the dosing (Mithoefer et al. 2003). However, in 2003, the study was retracted amid controversy when it was revealed that due to mislabeling, methamphetamine and not MDMA (Ecstasy) had been administered in the laboratory (Ricaurte et al. 2003). The retraction unleashed criticism at Ricaurte and McCann's larger research program, and drew attention in the media to other methodological issues with their studies (McNeil 2003). Fears around MDMA (Ecstasy)'s neurotoxicity began to wane as new studies found that changes were short term, and almost non-existent in moderate MDMA (Ecstasy) users. A study looking at a unique population of MDMA (Ecstasy) users who had low rates of use for alcohol, marijuana, or other drugs, found that moderate use of MDMA (Ecstasy) had no effect on neurocognitive performance (Halpern et al. 2004).

The debate over MDMA (Ecstasy)'s neurotoxicity delayed the initiation of MAPS' clinical development program for several years. While the FDA approved MAPS' "proof of principle" study for MDMA-assisted therapy in 2001, the study itself was not initiated for another three years due in part to difficulties in finding an Institutional Review Board (IRB) to oversee the study. MAPS submitted to eight different IRB boards, had approval rescinded from one IRB due to the article in *Science*, and had begun considering forming their own IRB to supervise their research, before the article in *Science* was retracted (Schroder 2014). An IRB approved their study that same month, and MAPS' moved forward with initiating their first clinical trial.

While the neurotoxicity debates have been largely put to rest, MAPS studies must still answer to the questions raised around short-term safety during the late 1990s. Can the purity of the drug, the safety of the setting, and the moderation of the doses prevent issues around overheating and water intoxication? Are there adverse effects that have not yet been documented for this particular study population and for this method of administration? In the next section, I argue that for pure MDMA to be safe, the *documentary apparatus* must manage two sets of relations: first of bodies to drugs, and second of events and effects.

## Documenting the Trial

A few months into my fieldwork in MAPS offices in Santa Cruz, I received my first lesson in what I will refer to as the *documentary apparatus* of the clinical trial. I was working in the clinical team's small attic office under Beth's supervision on data entry conventions from a recently completed study in Switzerland. I was working at an older desktop computer shared by interns, while Beth was on the opposite side of the room at her desk, which was specially outfitted with a port for her laptop and a large external screen, which often had multiple electronic documents laid open. I had turned around in my chair to talk through the project. We were working with case report forms (CRFs), but Beth kept talking about source documents. Confused, I asked for clarification, "What is the difference between a source document and a CRF?" Without missing a beat, Beth answered, "The first time pen touches paper that is the source. If a nurse writes the blood pressure on a sticky note, then that sticky note is the source document." She reached over and grabbed a piece of binder paper off her desk and began drawing as she talked:

> The source documents, which include all the tests and lab notes, stay at the study site. Information from the source documents is transferred to the CRFs, which are then moved back to the sponsor's offices after the study is closed out. Data from the CRFs is then entered into the database, which is what we are working on now.

I rolled my chair closer so I could watch over her shoulder as she drew a series of boxes and arrows connecting the site and source to CRFs, to the sponsor, and to the database. "The sponsor is responsible for monitoring both the source documents and the CRFs," she said as she drew an arrow back from the sponsor to the site, completing the circle. "We visit the site to make sure that source documents are being correctly filled out and that the information on the CRFs matches the source," she concluded, handing me the drawing to take back to my desk.

Source documents and CRFs are the cornerstone of data collection in a clinical trial, but they are just two parts of an entire apparatus of clinical documentation. There are also protocols, informed consent forms, the investigator brochure, standard operating procedures, drug accountability logs, and study reference manuals, to name just a few. During my fieldwork, the clinical team was constantly drafting and editing documents. Even though documents were individually drafted, they were always interrelated. Thus, descriptions of study visits in protocols needed to match the descriptions of visits in the study reference manual and in the source documentation. The decision to change something as small as the window of time for a visit in the protocol could produce a domino effect requiring edits to a series of interrelated study documents.

Yes, the source document is the first time that pen touches paper, but Beth's definition doesn't fully capture the work that the source records perform. Source documents are monitored by a study's sponsor, and they are also subject to audit by the FDA (Lisook 1990). Thus, the source documents should recreate the study as it happens for auditors, or as one summation on good documentary practice admonished: "What is not documented is not done," and "Document what is done

as well as what is not done" (Bargaje 2011, 60). In short: Documents don't just inscribe test results, they also inscribe the practices and actions of researchers. Yes, as Beth described, they inscribe blood pressure, but they also inscribe the very act of collecting (or not!) the blood pressure.

In this section, I ethnographically track the production of source documents and analyze the interrelated work they perform in securing safety in the MDMA-clinical trials. I make two intersecting arguments about the work that documents perform in securing safety. First, I examine the work of documents in managing the relations of bodies to drugs by inscribing the practice of screening subjects into or out of the study. As I argue, pharmaceutical safety is tightly linked to the bodies that absorb the drug. Because a pharmaceutical's effects vary from body to body, the pharmaceutical also varies in its safety, thus, the documents that screen subjects are a key site for the production of safety. Second, to produce data on the safety of a drug, the documents must wrestle with the uncertain relationship between the drug and an event, such as a headache. I examine the use of documents to manage the relationship between effects and events. In both cases, I argue, safety as both data and practice does not emanate from the substance itself, but from the coordinated work of documents.

## Managing Bodies

In 2010, the FDA approved MAPS' protocol for a study of MDMA-assisted therapy for veterans with service-related PTSD. The Veterans' study, as it was called, would be the second MDMA-assisted therapy study sponsored by MAPS in the United States. The first study, the proof of principle study, investigated crime-related PTSD. In the yawning years between when the proof of principle study was approved in 2001, initiated in 2003, and finally closed out in 2009, the United States had sent soldiers into both Iraq and Afghanistan. Many of these veterans were returning with diagnoses of PTSD. The shift from crime-related PTSD to service-related PTSD was a strategic move by MAPS to tie the fate of MDMA to public calls for better psychiatric services for veterans.

The new study came with new screening criteria. These criteria not only define the study population, they are also a critical part of the production of safety within the trial. While inclusion criteria define the study population—in this case, treatment-resistant service-related PTSD—exclusion criteria are used to protect potential subjects for whom the treatment might pose too great a risk. For example, all pregnant women or nursing women were excluded from the study—as they usually are—because of the unknown risks to the fetus or infant. Clinical trial participants can have complex medical and psychiatric histories, and so the source documents must inscribe the search for both known conditions that are exclusion criteria, as well check for undiagnosed conditions. The exclusion criteria for the first proof of principle study were conservative, excluding a number of conditions documented in both controlled laboratory studies and in studies of the recreational use of MDMA (Ecstasy). Because MDMA (Ecstasy) raises the heart rate and blood pressure, potential subjects with coronary artery disease, hypertension, or vascular disease were excluded, as were subjects with a history of hyponatremia (water intoxication) or hyperthermia (overheating)—both documented effects of the recreational use of

MDMA (Ecstasy). In addition, subjects with hepatic (liver) disease were also excluded because it was documented in relationship to recreational use of MDMA (Ecstasy).

Inclusion and exclusion criteria can be negotiated between a sponsor and the FDA. In this case, MAPS wanted to expand the population eligible to participate in the Veterans' study to ease difficulties they had faced recruiting subjects in the proof of principle study. On the basis of the strength of the safety data from the first study, MAPS was able to renegotiate two conditions: hypertension and Hepatitis C. In the Veterans' study, subjects with asymptomatic Hepatitis C who underwent additional screening were allowed to enroll, along with those with controlled hypertension.

The fact that pharmaceutical effects vary in relation to the body that absorbs the drug is the very premise of exclusion criteria. What is safe for one body is not necessarily safe for another. Drawing on the language of philosopher of science A. N. Whitehead, Andrew Barry has argued for a redefining of chemical materiality as a historic route of associations (Barry 2005) To put it simply, associations rather than structures define chemical properties. In this case, the different associations of the drug with different bodies produce different properties for the pharmaceutical. Thalidomide is an excellent historical example. While the ingestion of thalidomide by pregnant women may have led to a wave of birth defects and the restructuring of the bureaucratic supervision of clinical research at midcentury (Marks 2000), thalidomide is still used as a treatment for leprosy and cancer (Matthews and McCoy 2003; Tseng et al. 1996). The safety of thalidomide lies not in the substance itself, but in the relation between particular bodies and the drug.

The new exclusion criteria meant that the clinical trial team needed to generate new source records to guide the screening process. MAPS' source records often provided guidance for the investigators, frequently reminding them of procedures from the study protocol. In collaboration with the investigator, the clinical team needed to develop new source records providing proper documentation and instruction for the partial inclusion of Hepatitis C and hypertension. In this case, a worksheet was developed with boxes that could be checked if a subject had Hepatitis C, and then that could be checked as additional laboratory tests were completed. Or if the subject had hypertension, documents that could indicate that the symptoms were under control.

The Veterans' study source documents for the screening of subjects were fourteen pages long. Adding the worksheet was a relatively minor endeavor, and the clinical team was able to quickly integrate the changes into the structure of the document itself. First, the clinical team designed a short flowchart on the seventh page of the screening source documents, which guided the investigators through the requests for extra tests. Then, the new labs were added to a checklist on the first page. And, finally, on the final page of the screening records—where there was another check list reviewing all exclusion criteria—the clinical team added a bolded statement asking the investigators to check if further testing was done in the case of both hypertension and Hepatitis C.

However, as detailed as the additions were, the checklist would not be included when information was transferred from the source to the CRF. While source records must recreate the study as it happened for auditors, CRFs condense the information collected by investigators into a manageable subset, which will be entered into the

database for analysis. Thus, not all the details of the labs and testing collected at screening would become data. These documents did a different kind of work. The worksheets in the source records transform those carefully negotiated exclusion criteria in the protocol into a set of *practices* with a documentary trail, which potential auditors could follow. And more significantly, this kind of documentation is the *very premise of the data itself*. When MAPS says that MDMA has been administered safely in laboratory settings, that safety is premised on a relation. Safe for a body with controlled hypertension. Safe for a body without a history of hyperthermia or hypnonatermia. If the distinction between MDMA and Ecstasy rests on safety, then the attention paid to screening criteria underscores the fact that safety doesn't emanate from the substance itself, but from the relation of the substance to the body that absorbs it. Documents inscribe the production of those relations, rendering them traceable, even if they do not become data.

## When Is an Event an Effect?

While the screening documents manage the relation between bodies and drugs, once absorbed the focus of the documents changes. Since the pharmaceutical disappears, what the documents inscribe during the trial is not the drug itself but events that manifest in the body that absorbed the drug. However, bodies are constantly changing, fluctuating, in response to all kinds of things. Sometimes, the cause seems clear. For example, the headache that manifests after not drinking water, or the swollen fingers after a meal heavy in sodium. Other times, however, the cause of these events is not so clear. Eyes can become dry or itchy with the changing levels of pollen in the air, or after a bad night of sleep. The critical question in documenting safety data is: Which changes, which events, are actually effects of the drug in question?

In this section, I examine how the *documentary apparatus* manages the relation of events and effects. As I will discuss, not every event is an effect of the drug and not every effect is an event. As I have pointed out, safety is twice baked into the clinical trial documentation. The monitoring of blood pressure is both a safety practice and part of the collection of safety data. However, what makes safety even more complicated in the clinical documents is that safety is a difficult category to limit. While the clinical efficacy of MDMA for PTSD is being assessed through a primary outcome measure—the Clinicians Administered PSTD Scale—there is no single scale or measurement for safety. This is in part because safety is not tracked through a single measurement, but a series of interrelated categories, buttressed by specific measurements. Safety data are structured around the collection of adverse events (AEs)—a regulatory category with the broad definition of "Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment" (International Conference on Harmonization 1995). As I will discuss further, the clinical documents further broke AEs down into both unexpected AEs and spontaneously reported reactions, which were AEs that had already been observed in published studies in connection with MDMA (Ecstasy).

The distinctive temporal pacing of drug administration in the MDMA studies worked to the advantage of researchers in demarcating events that may be related to MDMA. For example, in the clinical trials used to approve Zoloft (Sertraline) as a

treatment for PTSD, subjects were administered a flexible dosage of 50–200 mg *daily* over the course of 12 weeks—longer if they chose to continue to the open label phase of the study (Brady et al. 2000). In contrast, subjects in MAPS-sponsored MDMA studies receive MDMA on just two or three occasions. Experimental sessions—when subjects receive MDMA or placebo—are spaced about a month apart with a series of talk therapy or integrative sessions conducted in the interim. The experimental sessions take place in a controlled setting—usually a therapist's office—under the supervision of a co-therapist team. The temporal and physical spacing of these experimental sessions allowed for detailed documentary work. The therapists both guide the session and carefully monitor the subject's vital signs—blood pressure, pulse, and body temperature—as well as signs of psychological distress using a single-item rating scale, the Subjective Units of Distress scale. Subjects remain overnight at the therapist's office after experimental sessions and have daily monitoring phone calls with the therapists in the seven days following.

After a year of working with the clinical team, I was tasked with creating source documents and CRFs for an extension study. The study would assess the benefits of an additional experimental session with MDMA for subjects from the proof of principle study who had experienced a relapse in symptoms of PTSD. Of course, I wouldn't be inventing the source and CRFs from scratch. Rather, Beth told me to modify already drafted source and CRFs from the Veterans' study, which had the most up-to-date study language, using the extension study's protocol as my guide.

Creating the source and CRFs involved cutting down and then pasting sections of the Veterans' study's more elaborate study documentation to fit the limited parameters of the extension study's protocol. As I worked, I kept the extension study's protocol open on my computer alongside the source documents and CRFs, reading through descriptions of the different visits and ensuring that the steps outlined therein were reflected in the source records. Cutting and pasting was necessary because the clinical team had developed a number of detailed charts for collecting blood pressure, heart rate, and body temperature, which needed to be retained exactly as specified in the protocols.

These charts were central to demonstrating that MDMA produced effects that were not safety events, or more specifically, AEs. As mentioned, two central safety concerns around MDMA were hyperthermia (overheating) and cardiovascular events. Hyperthermia is well documented in the literature on recreational users of MDMA (Ecstasy); and, because MDMA (Ecstasy) raises heart rate and blood pressure, there have been concerns that this will lead to cardiovascular AEs. In accordance with study protocols, subjects' heart rate, blood pressure, and body temperature were monitored at highly specific intervals. These charts allowed MAPS to collect detailed data on what MDMA's effects were for these physiological indicators.

While the blood pressure monitor and other machines might produce the readings, it is the charts that produce the standardized intervals of results that could be compared across subjects. In the compilation of the data inscribed on these charts and then compared between the placebo and treatment groups after unblinding, MAPS has found that MDMA has a measurable effect on blood pressure and heart rate. However, these changes in the body, these effects, have been well tolerated by most subjects as measured through the collection of AEs. AEs are collected on

a special form that was attached as an addendum to the main body of the source documents. As such, the AE page could be filled out at any time and copied over and over again to record as many AEs as needed documentation during the study. So, if a subject's blood pressure went so high as to require medical intervention, not only would the elevation in blood pressure be recorded on the chart, the event itself would also be recorded on the AE page. In discussing the safety data, MAPS stated that while blood pressure and pulse were elevated during MDMA sessions, these effects were transient and self-limiting and

> are likely to be well tolerated by healthy individuals. . . . It is noteworthy that, although there was one, moderate, expected cardiac AE that was deemed serious because it led to overnight monitoring of increased ventricular extrasystoles, no severe cardiac, renal and urinary, or vascular disorders were reported, and they were also the least frequently reported types of AEs after any MDMA dose. (MDMA Investigator's Brochure 2018)

Thus, the safety claim works through the coordination of data from the chart and data from the collection of AEs. While data collected from the chart indicate that MDMA produces an effect, the data from the AE page indicate that the effects themselves do not rise to the level of safety events. It is through the combined work of the two documents that MAPS can claim that MDMA produces an effect that is not a safety event.

In addition to the charts for recording vital signs and AEs, the researchers had designed another chart that tracked spontaneously reported reactions, also referred to as expected AEs. Spontaneously reported reactions were collected during a tightly limited time frame: on the day of the experimental session and for the seven days following. Unlike the open form for the collection of AEs, spontaneous reported reactions were collected on a chart on which the events were already listed. In the proof of principle study, the events were selected based on a review of the existing literature on both MDMA and MDMA (Ecstasy). For the purposes of the collection of safety data, the reactions are spontaneously reported, but their collection has been carefully calculated in advance of the study.

As I created the source and CRFs, I copied the spontaneous reported reactions chart from the Veterans' study. It listed 27 possible effects of MDMA: anxiety, diarrhea, difficulty concentrating, dizziness, drowsiness, dry mouth, fatigue, headache, heavy legs, impaired judgment, impaired gait/balance, increased irritability, insomnia, jaw clenching, tight jaw, lack of appetite, low mood, muscle tension, nausea, need for more sleep, nystagmus, parasthesias, perspiration, restlessness, ruminations, sensitivity to cold, thirst, weakness. The chart included a space for recording the intensity of the reaction. At the top of a chart, a small box marked "none" reminded the investigators to document the absence of reactions. However, as I checked back to the protocol for the original proof of principle study, only 24 spontaneous reported reactions had been monitored. After reading other study documents, I learned that after a review of the AEs recorded during the proof of principle study and a comparison of the events in the placebo and treatment group after unblinding, three new spontaneous reported reactions were added to the chart and collected in subsequent studies: diarrhea, impaired judgment, and muscle tightness.

Thus, as I was creating source documents for the extension study, I was integrating a new chart, which was based on data produced in the original study. As the studies had collected data, new parameters for safety data had emerged, which had changed the *documentary apparatus*.

Unlike the effects that are not safety events—blood pressure and heart rate—the collection of new spontaneously reported reactions like diarrhea, impaired judgment, and muscle tightness demonstrates the coordinated work of documents in rendering traceable the uncertain relation between event and effect. All three events had emerged first as AEs in the proof of principle study, were deemed "probably related" by investigators, and after unblinding, occurred more frequently in the MDMA group than in the placebo group. However, the recording of an individual spontaneously reported reaction on its own does not deem an event an effect. Producing the link requires standardization and comparison of many events across many subjects in different treatment conditions. In discussions of the safety data, MAPS' researchers point out that events like "anxiety" occur in both subjects receiving both MDMA and placebo (MDMA Investigator's Brochure 2018). Thus, the anxiety may be related to the underlying PTSD and not necessarily MDMA. No single event is necessarily an effect of MDMA. Or, to put it another way, the substance itself doesn't determine that an event is an effect. Rather, it is only through the collection of many events on this standardized chart that the totality can be analyzed and a possible relation between an event and MDMA be postulated. Thus, the relation between drug and event emerges not from the substance itself but from the work of the documentary apparatus.

## Leaky Pharmaceuticals

In 2010, as I began my fieldwork, MAPS clinical team was revising and restructuring the investigator's brochure (IB) to fit the guidelines for the International Conference on Harmonization Good Clinical Practice (ICH-GCP)—a set of conventions to standardize the production of clinical documents and thus the collection of clinical data. (As Kaushik Sunder Rajan has pointed out, the "harmonization" of the ICH-GCP is central to the global hegemony of the multi-national pharmaceutical industry [Rajan 2017].) As the sponsor of the MDMA trials, MAPS is responsible for maintaining the IB, which summarizes all research on the investigational product (IP). The IB must include basic information on the structure of the substance, as well as an up-to-date summary of all studies on its pharmacological and toxicological effects, any clinical studies on its safety and efficacy, and a description of all known risks and side effects (21 CFR 312.23(a)(5)). Notably, the IB for MDMA reviews data derived from studies on MDMA as well as MDMA (Ecstasy), even though, as researchers said: "That is not what we are studying."

One of the critical tasks for the revision was drafting a new section: "Safety and Efficacy of MDMA-assisted psychotherapy for PTSD." The previous version of the IB had been published in 2007 prior to the closeout of the proof of principle study. Thus, this edition of the IB would be the first to include data from MAPS' own clinical studies. The section on efficacy was only four paragraphs long—a page at most—while the safety section sprawled across eight pages of detailed charts comparing safety data for the placebo and MDMA groups analyzed after

unblinding. Blood pressure, body temperature, and pulse were broken down by both averages and peak values; Spontaneously reported reactions were detailed first on the day of the experimental session and then in the seven days following; more charts still detailed the unexpected AEs that were deemed possibly related by investigators prior to unblinding. The efficacy data could be quickly summarized because it comes down to a single effect manifesting through a specifically chosen study measure and then compared between the placebo and treatment group. In contrast, the summation of the safety data must wrestle with multiple measurements of effects and attempt to account for an entire array of events.

Every few years, MAPS publishes an updated IB, revising these charts. These data are the outcome of information inscribed on source records, transferred to CRFs, entered into the database, and then analyzed through the comparison of the placebo to treatment groups after unblinding. Slowly, the section on the safety of MDMA-assisted therapy lengthens, and the case that MDMA can be administered without serious adverse events (SAEs) grows. However, if the safety data had not manifested as MAPS was hoping; if there had been widespread SAEs related to the drug; in short, if the data did not support the claim that MDMA could be administered safely in controlled laboratory settings, then the distinction that MAPS is trying to make between MDMA and Ecstasy would have fallen apart.

If pharmaceuticals are leaky things, which take effect though their entanglement with our bodies; if their efficacy requires dissolution and absorption in relation to particular bodies, then to circulate as a regulated, commoditized object, these relations need to be managed. I have argued that the documentary apparatus provides critical work around this leakiness by managing the relation between bodies and drugs and events and effects. Hayden has argued the pharmaceutical research works by proliferating materials by "producing and recontextualizing chemical compounds as simultaneously the same, and not the same" (2012, 271). In this reading, MAPS is not isolating MDMA, but is rather producing a new material, with a new safety profile. MDMA's safety doesn't emanate from the substance alone, but from the entanglement of documents and research practices that screen bodies, space out doses, monitor heart rates, and documents AEs. To return to the original statement that MDMA is not the same thing as Ecstasy, in MAPS' bifurcation MDMA is a safe, stable, chemical singularity that is being clinically investigated, while Ecstasy is a messy multiplicity that is haunted by a constant uncertainty about its chemical identity and the circumstances of use. However, this article has argued that the distinction in *substances* follows from a distinction in *safety;* wherein safety is a product not of substance but of relations. It isn't that because MDMA is pure it is safe, but that as the clinical trials manage relations through documents, MDMA can become distinct from Ecstasy.

## Note

*Acknowledgments.* This article has existed in a number of forms, which have been commented on by many generous friends and scholars. Most notably, it has been shaped by the thoughtful comments and guidance of Cori Hayden and Kevin Karpiak, as well as the two anonymous reviewers. Different versions of this article

were substantially improved by comments at the STS@OSU Workshop, the Social–Cultural Workshop in the University of Michigan's Anthropology Department as well as the Cultures of Science and Technology Working Group at The Ohio State University. Research for this article was supported by the Wenner-Gren Foundation.

1. The social, regulatory, and academic entanglement of the terms MDMA and Ecstasy makes following a set naming convention when writing about its history difficult. For instance, the Drug Abuse Warning Network (DAWN) program tracks mentions of Ecstasy in emergency rooms, while the U.S. customs agency tracks seizures of MDMA. To lessen confusion for readers, when writing about MAPS' clinical trial program and the clinical use of the drug, I have chosen to follow my informants in their use of MDMA to refer to their investigational product (IP). However, when writing about other contexts where the use of both terms overlaps, I have chosen to use MDMA (Ecstasy) as a standard reference.

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