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"Ready for What?": Timing and Speculation in Alzheimer's Disease Drug Development

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Abstract

"Readiness cohorts" are an innovation in clinical trial design to tackle the scarcity of time and people in drug studies. This has emerged in response to the challenges of recruiting the "right" research participants at the "right time" in the context of precision medicine. In this paper, we consider how the achievement of "readiness" aligns temporalities, biologies, and market processes of pharmaceutical innovation: how the promise of "willing bodies" in research emerges in relation to intertwined economic and biological time imperatives. Drawing on long-term engagement with the field of Alzheimer's disease prevention and interviews with researchers from academia and the pharmaceutical industry, we describe the discursive construction and practical arrangement of readiness. This paper contributes to understandings of temporal specificity, or "timing," within

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prevention research and casts critical light on the way this specificity—the threshold for "trial readiness"—relates to an opaque and highly speculative drug development pipeline. Extending the study of biomedical potential, as that which holds promise but may not yet exist, we consider how absences operate in adaptive trials. By highlighting these absences ("ready for what?"), we outline an opportunity for socio-ethical research to intervene in the speculative gaps of drug development.

Keywords
clinical trials, Alzheimer's disease, ethics, speculation, time, readiness

Introduction

Time is a scarce resource in the world of clinical trials, in which timelines for recruiting and conducting trials present significant challenges (Montgomery 2017). In addition, the *timing* of disease progression has an increased significance in the growing number of trials focusing on preventative therapies, which rely on early detection of biomarkers (Kerr et al. 2019; Swallow 2020) as "silent" indicators of risk (Dumit 2012a). Such pressures have contributed to the emergence of new clinical trial practices, including "adaptive" methods (Montgomery 2017) and practices of "recruitmentology" that promise increased efficiency in clinical trials and the expansion of study populations (Fisher 2007; Epstein 2008). However, as Montgomery and Pool (2017, 2) point out, the "experimental publics" of clinical trials are partial, emergent, and temporally contingent; they "enact and are enacted in relation to the research practices they are presumed to pre-exist".

In this paper, we examine challenges of time and recruitment in the context of the move to precision or stratified medicine, focusing on "readiness": the state of being ready to participate in, or launch, a pharmaceutical drug trial. We explore the dynamic configuration of experimental publics from the perspective of pharmaceutical innovation and its intersection with longitudinal research (Mitchell and Waldby 2009). We consider how the creation and coordination of readiness involves aligning specific time points along biological trajectories and market processes of pharmaceutical innovation. In doing so, we show how the promise of "willing bodies" in research emerges in relation to intertwined economic and biological time imperatives in drug development: the pursuit of a future in which disease is caught "early" and progression stopped "quickly."

Our paper draws on a five-year engagement with the case and a series of expert interviews with researchers from academia and the pharmaceutical industry involved in preparing a phase II clinical trial. Our purpose is to demonstrate how readiness is defined and enacted: what or who determines change through time, and where are the thresholds of readiness in biological and drug development trajectories? By examining the operationalization and practical arrangements of readiness in clinical trials from the perspective of experts in this field, we seek to understand the concept of readiness as both an analytic and an object of study (Taussig, Hoeyer, and Helmreich 2013). This paper thus contributes to our understanding of temporal specificity, or "timing," within prevention research, particularly in the dementia field where time is crucial to both the conceptualization of disease trajectories and the organization of pharmaceutical drug trials. It also casts a critical light on the way this temporal specificity—the threshold for "trial readiness"—emerges in relation to an opaque and highly speculative drug development pipeline.

In the following sections, we locate readiness within wider thinking about temporality, biomedicine, and techno-scientific progress before going on to introduce the Alzheimer's disease research context, our specific case, and our methodology. The empirical material then explores the discursive construction and practices of producing readiness: first, as a state within the brains and minds of study participants, who thus become "trial-ready" subjects; then, as a broader sociotechnical arrangement including (the potential of) pharmaceutical drugs; and finally, as an achievement of speculative, anticipatory practices between the drug development pipeline and on-the-ground clinical research. In concluding, we consider how socio-ethical interventions can open up the "speculative gaps" we identify to make space for other (neglected) actors, tools, and stories within the field of Alzheimer's research.

Conceptualizing Readiness

Moving away from narratives of naturalized trajectories of decline and intervention that dominate Alzheimer's disease research, we are interested in the temporal *organization* of bodies, brains, technologies, and drugs. In our research, readiness pertains to a particular point in the aging process within potential trial participants, but it also speaks more broadly to the sociotechnical organization of time in drug development and neurological research. Following trends in trial research, the European Prevention of Alzheimer's Dementia (EPAD) study operates from a future-oriented

position, shoring up disease modeling and other biostatistical methods to anticipate the need to adapt the design or let drugs "fail quicker" (Montgomery 2017). Given the aforementioned conditions of time-sensitive interventions and economic time pressures, the logics of a readiness cohort in Alzheimer's disease research are about *organizing* and *optimizing* the temporalities of both the disease and drug development. These logics bring readiness into contact (and contrast) with vocabularies of future orientation in techno-scientific contexts such as notions of timing (Brown 2000), anticipation (Adams, Murphy, and Clarke 2009), potentiality (Taussig, Hoeyer, and Helmreich 2013), and speculation (Bryant and Knight 2019; Wilkie, Savransky, and Rosengarten 2017).

In describing this organization and optimization of temporalities, we attend to what is present, what is absent, and what is "not yet" when it comes to disease trajectories and drug development. Dumit's (2012b) work on thresholds for "at-risk states" is helpful for understanding readiness as a function of disease trajectories. His description of health and illness on a continuum, with a decided-upon line between them, is illuminating in a field (such as Alzheimer's disease) where these lines are often redefined; in Dumit's words, "the line is determined not by overt pathology but by *clinical trials*" (p. 105, our emphasis). As we go on to describe in more detail, this threshold line has been shifted from the clinical stage of dementia (symptomatic) to the preclinical period ("no symptoms *yet*"). Already it is becoming clear that in setting the threshold for trial readiness in Alzheimer's disease research, *timing* is everything.

This story contains another "not yet," which is crucial to conceptualizing readiness. At the time we carried out the research (and as we write), there was no existing treatment to halt or reverse the effects of dementia. Moreover, the specific intervention was yet to be secured within the project, making the intervention drug a "manifest absence" in this particular trial platform (Law 2004, 83). However, given that such absences are "always potentially contestable" (Law 2004, 83), we explore how objects and people work together or in tension to bring *possible futures* into the present (Wilkie, Savransky, and Rosengarten 2017). Here, we draw on Bryant and Knight's (2019) discussion of *speculation* as a future-oriented engagement with absence or "gaps." For example, we think with the case study in which investments in speculative futures transform "no oil" into public rhetoric of "no oil yet" (Weszkalnys 2015, in Bryant and Knight 2019, 98). In our context, how might the future-oriented logics of readiness transform the current predicament of "no drugs" into a rhetoric of "no drugs *yet*?"

In a similar vein, the concept of *potential* opens up analyses of that which holds promise but may not yet exist (Gibbon 2013; Taussig, Hoeyer, and Helmreich 2013)—a logic that may explain hopeful attitudes toward drugs that keep being produced and tested but do not yet exist as viable treatments. It is here, in the work of narrating scientific progress, that we see the "practical orchestration of present problems and future solutions" described by Brown (2000, 89) in his "breakthrough motif." Of particular interest to our conceptualization of readiness as comprising *temporal specificity* and *potential* is Brown's use of the rhetorical notion of "Kairotic moments" (Brown 2000, 89), which are constructed as *the right time* for action (both by making predictions about the future in an anticipatory mode and by narrating events in retrospect (Brown and Michael 2003). If readiness marks the *right time* for pharmaceutical intervention, what makes this moment "right?" And why is this interesting both empirically and conceptually? Following Taussig, Hoeyer, and Helmreich's (2013) approach to an "anthropology of potentiality," we explore how readiness operates as both an object of study and an analytic.

"Reengineering" Alzheimer's Disease Prevention

Our paper concentrates on pharmaceutical research in the context of Alzheimer's disease. Despite intensive efforts, two decades of clinical trials in Alzheimer's disease have yet to identify a drug that is able to change the course of the disease. In response, there has been what researchers describe as a "paradigm shift," from curing symptomatic disease to preventing the emergence of symptoms, and concurrently, from a model of disease based on clinical and behavioral symptoms to one that privileges biological signs and changes in these (Lock 2013; Milne and Latimer 2019).

In a field so troubled by repeated failure, the cultivation of future promise in Alzheimer's research has involved reinforcing the biological framing of disease in the hope that this might improve the accuracy of prediction (Swallow 2020). Where research and trials previously targeted people who had the disease in the hope that they could eventually mitigate or reverse the effects of the disease, the emerging "preventative assemblage" (Niewöhner et al. 2011) of Alzheimer's disease now seeks to treat people who do not yet have the disease but are "at risk" (Lock 2011; Leibing 2014). The current consensus in the neuroscience and clinical trials community is that the main problem with previous pharmaceutical therapies is that they have not caught the disease *early* enough or in *subtle* enough ways (Molinuevo et al. 2016). To date, this approach has met with little success; the value of tracking and

targeting biomarkers (understood as biological proxies of "predisease" states) remains hotly contested (Frisoni and Visser 2015). Nevertheless, the "anticipatory politics" (Jae 2018) of early detection and pharmaceutical prevention is sufficient to mobilize a whole field of disease-modifying clinical trials for Alzheimer's. Such trials necessarily involve people who do not fulfill symptomatic criteria for disease and who may consequently neither be seeking treatment nor accessing healthcare (Molinuevo et al. 2016).

The changing goals of clinical trial research have been accompanied by a shift in approach. Conventional models of clinical trials have been described by leading figures in Alzheimer's disease research as "broken" (Cummings et al. 2016). New approaches thus involve not only a fundamental "reengineering" of the nature of the disease being targeted (Cummings et al. 2016) but also new forms of measurement, revised regulatory guidance related to the goals and outcomes of trials, new collaborations between public and private sectors, and innovative trial designs that aim to speed the trial process and deliver results more quickly (Aisen et al. 2016; European Medicines Agency 2014). The move toward involving "minimally affected optimally selected study participants" (Jimenez-Maggiora et al. 2020, 226) aims to bring *temporal specificity* and, therefore *efficiency*, to the costly and time-consuming process of selecting, screening, and recruiting potential participants.

At the core of these interconnected shifts is the alignment of a diverse group of socio-technical actors concerned with identifying the appropriate moment in the temporal progression of the disease for techno-scientific intervention. The model, as elaborated by influential clinical trialists in Alzheimer's disease, involves "accelerating" the clinical trial process (Aisen et al. 2016); effective "subject selection" (Vellas et al. 2011) and "stratification" (Carrillo et al. 2013) of the research population; and "large-scale co-operation" among the actors involved in funding, conducting, and regulating Alzheimer's disease drug research (Aisen 2009).

The EPAD Study

We attend to a particular manifestation of these temporal concerns and practical realignments, within a large-scale project: the EPAD study. EPAD is one of a number of public–private collaborations in Alzheimer's disease research funded through the European Innovative Medicines Initiative (IMI). It was established as a result of the IMI's "European Platform for Proof of Concept for Prevention in Alzheimer's Disease" (EPOC-AD) call.

IMI topic areas are determined in line with recommendations from industry to address "bottlenecks" in drug development and are intended to create the potential for precompetitive collaboration between large and small biotech and pharmaceutical companies (Goldman 2011), although as IMI leaders acknowledge, the boundaries of what constitutes "precompetitive" are neither clear nor static (Goldman 2011; Laverty and Meulien 2019).

The EPOC-AD call described the IMI's intention to invest €25 million—with an equivalent contribution from EFPIA—to create a "precompetitive space to enable collaboration for optimizing patient selection, clinical trials methodologies, and candidate therapies" (Innovative Medicines Initiative 2013, 19). The call describes how this would "de-risk the enterprise" of Alzheimer's disease drug development (Innovative Medicines Initiative 2013, 29), by creating a platform that would not benefit any single program of drug development but would be available for simultaneous use by otherwise competing companies. Initial industry involvement in the project included commitments from a number of large and smaller pharmaceutical companies including Janssen, Eisai, Roche, AbbVie, AC-IMMUNE, Amgen, Astellas, BIOGEN IDEC, Boehringer Ingelheim, Lundbeck, Pfizer, and UCB (Innovative Medicines Initiative 2013, 32). These companies were involved to differing extents in the development of the project and, indeed, in Alzheimer's drug development overall (Cummings et al. 2017). However, by participating in the IMI call, each could expect to be able to shape and use the potential EPAD platform.

The value to industry of the EPOC-AD/EPAD approach was described in a mid-2013 workshop held by the New York Academy of Sciences. Michael Ropacki of Janssen Alzheimer Immunotherapy set out a "Registry Recycling Model," in which individuals would be enrolled in an observational cohort study, from which

> Clinical studies can then draw . . . to create a population of well-characterized subjects, *shortening the enrolment period and increasing both the efficiency and efficacy of trials*. (Bain 2013, our emphasis)

At an Organisation for Economic Co-operation and Development (OECD) workshop held shortly after the EPOC-AD call, Luc Truyen (also of Janssen) described how the EPAD program would create "a standing trial ready platform combining direct access to well characterized subjects with sites certified and ready to engage trial participants" (OECD 2015, 19). Readiness was thus central to the conceptualization and establishment of the EPAD program and continues to inform the development of initiatives such

as the Trial Ready Cohort for the Prevention of Alzheimer's Disease, which champions the "minimally affected optimally selected" recruitment approach referenced above (Jimenez-Maggiora et al. 2020). Thus, EPAD was one of several initiatives seeking to minimize the investment of time and money in recruiting eligible participants and to "beat the (biological) clock" when it comes to intervening in disease progression. Here, the stage is set for the launch of the readiness cohort by members of a core group of actors who were defining the terms and setting up the conditions for this cohort to become a population of potential trial participants.

Given its centrality to the reimagining of Alzheimer's disease trials occurring through these initiatives, we propose that the construction of readiness—the *right moment* for the *right individual* to respond *optimally* to a given drug—warrants close empirical investigation. Our discussion draws on our work in social science and ethics embedded within the EPAD study. This work on "ethical, legal and social implications" (ELSI) concentrates on new approaches to clinical trial recruitment and the move to focus on asymptomatic or mildly symptomatic populations in Alzheimer's disease research (Milne et al. 2017). Enacting our role as (post-)ELSI researchers (Balmer et al. 2015), we carried out this study as observers of, and researchers within, EPAD. We draw on continuous involvement in the study since its inception, and eleven expert interviews with scientific researchers (from research assistants to the study's executive committee) and pharmaceutical industry partners, exploring perspectives on what readiness "is" and how it was being "done" throughout the EPAD infrastructure. These data were generated at a crucial moment in the project, in which actors were preparing to launch a phase II clinical trial after several years of observational research on Alzheimer's disease trajectories. We begin by exploring how readiness was defined, before drawing out how specific thresholds for readiness emerged in practice and the speculative work involved in managing the drug development pipeline.

Part I: Readying Participants

"Readiness is . . ." a dual definition

> So, I would define it as people who are ready to go into interventional studies; people who are both ready from a biomarker point of view, so they have the biomarkers of Alzheimer's disease, but also people who are ready . . . I guess mentally? (Trial coordinator)

In interviews between meeting sessions on the science and practicalities of the future trial, one of the first questions we would ask was "what is 'readiness' in the context of the 'readiness cohort?'" The starting point of responses coalesced around two aspects of readiness: a (bio)technical aspect and a psychological or "mental" one, both located within the individual. The (bio)technical aspect (hereafter "technical" readiness) was, as the trial coordinator above put it, about being ready to participate in a drug trial "from a biomarker point of view." This corresponded to the inclusion and exclusion criteria of the study and, as another trial coordinator called it, "that aspect of ticking the boxes of a trial." The psychological aspect, on the other hand, was about (potential) participants' willingness, consent, and engagement—emotional and intellectual—with the idea of being in a pharmaceutical drug trial. According to these accounts, individual subjects became ready in two ways—in brains and in minds—as the study progressed toward launching the trial. We take this dual definition as a point of departure for thinking about how readiness is understood and operationalized throughout the study and the future trial.

Although psychological readiness was considered in terms of individual volition and cognition, this state of mind (and its maintenance) had implications throughout the study. Psychological readiness is crucial, not just because of the rights and well-being of participants but because of what is at stake if participants drop out. There is no threshold at which psychological readiness has been definitively achieved; it is a state that has to be sustained and maintained. As a US-based industry representative stressed, "maybe even the worst thing that can happen is you actually enroll somebody and then they drop out." He went on:

> Because you've invested the quarter of a million dollars of time and money of all the professionals and the sponsor to get that person qualified to be in that trial. And then because they weren't emotionally committed to it, or their caregivers weren't, they drop out.

His comments make clear the value of "readying" work through the clinical trials enterprise. Trialists took seriously the fragility of people's motivations to participate, be it altruism or hopes for access to successful disease-modifying treatment (or, in the words of the US industry representative, "love of self, love of family, love of country"). The possibility of participants dropping out hung heavily over everyone who had invested in the trial—financially, emotionally, and scientifically.

"That's why we do epad—to understand the timing"

Closely related to the within-*person* aspect of readiness was the within-*brain* aspect. In contrast to psychological readiness, there were quantitative measurements and thresholds for the technical, "tick-box" aspect of readiness. Thresholds for technical readiness were based on two important measures: first, levels of the beta-amyloid in the brain, the protein most commonly implicated in the etiology of Alzheimer's disease and the target of most disease-modifying clinical trials to date; and second, the clinical dementia rating score, a wide-ranging assessment of cognitive function.

At the outset of a trial, the way thresholds function is *in theory* simple: participants must *meet* the first threshold (showing that enough beta-amyloid has built up in the brain) and they must *not exceed* the second (showing that they do not have a dementia rating score of 1.0, which would mean they could be clinically diagnosed with dementia). These thresholds are important when planning a prevention drug trial because everything depends on understanding the nature and pace of change, and in so doing, framing the point in a disease process where a compound might most effectively "act." Indeed, one trial coordinator summed up the rationale for the project in terms of these temporal thresholds: "That's why we do EPAD—to understand the timing."

When it came to understanding the "timing" of Alzheimer's disease, there was a strong focus on the *very early* stages of the disease. But while some people talked of these early stages *being* the disease, others described them as more of a precursor: such as the industry partner who described them as "participants who have signals, with a higher risk." The technical thresholds set centrally by the project executive committee thus became pivotal to resolving these conceptual ambiguities and defining readiness. These technical readiness thresholds indicated an optimal moment for trial participation, when signs of pathology were considered to be most amenable to pharmaceutical intervention.

While psychological readiness was presented as socially produced and changeable, this technical aspect was "black-boxed" (Latour 1987) as a biological process within the brains of participants. In theory, reaching these fixed thresholds was contingent only on the timings and processes of the aging brain. However, in the following sections, we encounter aspects of readiness that were contingent on processes, people, and materials *beyond* the individual: a more distributed conceptualization of readiness than the initial descriptions suggested. As we go on to demonstrate, seemingly fixed thresholds were subject to alterations that reflected the

processes and politics of drug development. We focus on one particular threshold shift and contextualize it among the moving parts of the study.

Part II: Sociotechnical Coordination of Readiness

In opening up the "black box" of readiness thresholds, we found that considerable organization went into producing technical as well as psychological readiness. What is more, we saw ongoing adjustments to the study that shifted the threshold for readiness and therefore the status ("ready" or "not ready") of many cohort participants.

As we have described above, technical thresholds for readiness were in theory about having *crossed* the threshold for one key biomarker, beta-amyloid, and having *not yet crossed* the threshold for a clinical diagnosis for dementia. As a participant, you could, by this logic, only become "not ready" when you became clinically diagnosable with dementia. Having a diagnosis of dementia meant you would have passed the preclinical phase; it would be assumed there was no stopping the disease progressing, and therefore you would no longer meet the inclusion criteria for the trial.

In practice, however, there was another crucial way in which many people became "not ready" and therefore ineligible for the trial. In 2015, in the initial phases of the EPAD study, a core expectation was that future interventions would focus on people who had no symptom*s* of cognitive impairment at all but who *exceeded* a threshold for amyloid levels (referred to as "amyloid positive"). This reflected contemporaneous expectations about drug development, captured in the new guidance from regulators and the growing interest in studies among people without symptoms (European Medicines Agency 2014; Molinuevo et al. 2016). However, about three months before our interviews, this focus on completely symptomless or "silent" Alzheimer's disease changed, with consequences for all the other "readying" work that we have been describing. A trial coordinator explained this when asked about how recruitment was going in the context of these changes:

> Interviewee (I): of course, now we have a different kind of trial lined up, and that has changed the approach in EPAD dramatically. The idea that we had in our minds since the beginning was that we were focusing more on the *preclinical* phase of Alzheimer's. And that's what we've had in mind with recruiting as well. But now of course we've shifted our attention to MCI (Mild Cognitive Impairment) patients . . . . So that makes a huge difference for how to recruit and who to recruit.

Interviewer (NB):	At what moment did you feel "OK that really shifted?"
I:	Yeah, that's a good question. (The PI) sent out an email last couple of months ago, that was the official announcement that says, "we're really focusing on our efforts on MCI recruitment now," . . . Before that, I think it was communicated more between the lines.
NB:	OK, and how did the official announcement change things?
I:	It's all going to change now . . . before the message was: "OK, we're behind on recruitment, recruit as many as you can," and our programs were let loose . . . but now of course those people are—they're *less valuable* in terms of this specific trial.
NB:	So, it's like the terms of the readiness have shifted?
I:	Yeah, that's a good way of phrasing it.

This conversation charted the unfolding of an event that—confusingly—caused many people to become "not ready," without developing a clinical diagnosis of dementia. The initial focus on entirely preclinical (asymptomatic) Alzheimer's disease had given way to one that incorporated *mild* symptoms known as the prodromal phase of the disease. So, this was not about participants becoming ineligible for a trial because they had developed clinically diagnosable dementia. In fact, the participants who became "less ready" were those who were *more* cognitively healthy and who did not (yet) have signs of MCI. The reason for them becoming "not ready" was that *the terms of readiness had changed*. The threshold had moved further along the scale of cognitive decline to include the "prodromal" condition of MCI. The threshold had been destabilized, but it was clearly contingent on *something else*, aside from biology, psychology, or general scientific consensus.

Readiness is . . . in the drug?

> If you talk about trial readiness for if a *person* is ready—well that *depends on the compound* (Trial coordinator)

What was this "something else" that readiness was contingent on, beyond the biology and psychology of the participants in the readiness cohort? And what does this tell us about the values and materials that shaped and animated the project? The answer to the first part of this question emerged

throughout many of our interviews, usually soon after it became clear that criteria for becoming ready were more fluid in practice than in theory. Whether or not people were ready for *this* trial, we were told, was dependent on *what kind* of trial it was going to be and, specifically, on which *compound* the trial would be testing. As one industry partner involved in the operations of the study described, this meant that readiness *fluctuates over time*, as different drug owners come in with potential "interventions" for the trial:

> Yes, and indeed that point will differ over time again . . . readiness will look different in a year from now, in two years from now, because two interventions might come on board. A third intervention might come on board with all different expectations and eligibility criteria so then the readiness might look completely different. For instance, if the first PoC (Proof of Concept trial) will be let's say a prodromal subject, then you're kind of losing the readiness of the preclinical subjects because there is no PoC trial for them . . . . So, you see it kind of fluctuates.

This interview fragment describes exactly what the trial coordinator above was talking about, but this time, from an industry perspective. We hear about the moving parts of the trial responding to the kind of drug being added into the protocol. Earlier in the interview, she described the protocol as the "backbone" to the study, from which nothing could be removed but to which new trials could be added. It was one of these trials whose potential arrival set in motion the shift in the "terms of readiness," which made all of the asymptomatic subjects (with amyloid biomarkers) lose their status of being trial-ready.

The drug as actor: power and potentiality

Several people we spoke to across industry and academia echoed this idea of "flexibility," "fluctuation," or "fluency" in the operational definitions of readiness. Despite all the work that went into readying participants, to make sure they were willing to go into a drug trial and aware of the potential promise of that trial, there was always a chance that the *drug itself* would override this and make those very same participants ineligible for the trial (counterintuitively making them "become not ready").

Here, the creation of a readiness infrastructure oriented toward potential future trials disrupts conventional drug-development processes, in which trial development *follows*, rather than *precedes*, the existence of a potential

therapeutic agent. As a "precompetitive" collaboration aimed at establishing an infrastructure for trials, EPAD was at the mercy of the unfolding of "competitive" company development pathways. This contributed to concern about the power of the compound to technically "de-ready" participants who were psychologically "ready" to move into the trial. In such a situation, there was little that could be done to alter the "demands" of the drug.

How the drug acted on the trial platform and, in particular, the operationalization of readiness was distinctly future-oriented throughout the project. Unlike many of the more complex or subtle potential outcomes of EPAD, such as increased knowledge of how and why Alzheimer's disease develops in certain ways, the powerful potential of the drug was, quite simply, that it might *work*:

> People want to be part of this family, want to succeed, want to see eventually—does it work? I'm sure the drug companies want to see it working . . . we're all so disappointed with the failure of aducanumab[1] that we're going, *please let this work.*

These were the words of a recruitment team member, who had spent her career working with people with dementia and held huge hope for finding a cure. Other respondents were also concerned with the potential of the drug *working* but their accounts indicated varying degrees of influence over whether it would act in the desired way. Some were in a better position than others to manipulate the moving parts of the study to ensure the drug had the best possible chance of working and—more specifically—on *which particular types* of participants it might work best. For example, a biostatistician talked about finding the right (future) patient on which to *make the drug work.* When discussing the use of MCI as a proxy for trial readiness, he lamented the fact that trialists often tried to find these participants without more sophisticated predictive data to tell them whether or not these patients were "right." He insisted that through disease modeling, they could determine whether participants were on the "Alzheimer's pathway," whether they were "likely to progress," and whether they were "the right patient." For him, and others invested in the future trial, the potential of the drug was something to be predicted, modeled against data, and then cultivated through the selection of people *most likely to respond* to the compound available at any given time.

A story about the development of a clinical trial platform characterized by "flexibility," "fluctuation," or "fluency" bears little resemblance to the

broken "machine" in need of "reengineering" within the clinical trials literature (Cummings et al. 2016). Even more striking is the interdependency of different elements, namely, the way in which eligibility criteria, biological thresholds, and readiness itself both create the conditions for and respond to particular drugs. These drugs, therefore, came to be a driving force of the study, even as they remained an unconfirmed potential within the "pipeline" of potential pharmaceutical owners. In the final part of our findings, we attend to the temporal, future-oriented, and ultimately *speculative* nature of this driving force.

Part III: "Ready for What?" Animating Absence, Choreographing the Future

> So, we had to give a message that "there are going to be trials started somewhere in the course of EPAD, and the goal of that trial is to try to influence the course of Alzheimer's disease, but we're not really sure what it's going to be yet, and we're also not sure whether you will be eligible for it" . . . participants wanted to be ready, but *ready for what*? And at what time? (Trial coordinator)

We have hitherto described how thresholds of readiness were contingent on and responsive to the particular drug that was "in the pipeline" at any one time. In this final part, we follow the "moving parts" of the clinical trial—research—drug development nexus to the *speculative promise* of the candidate drug. The quote above illustrates the glaring unknowns surrounding the drug and its introduction into the trial: "ready, but ready for what?" Highlighting this speculative aspect of the trial, we consider how invisibilities and *absences* in the drug development pipeline operate in relation to the more *present* aspects of the study, and how we as researchers might work with speculation as a mode of engagement with the future of dementia prevention research.

The opacity of the drug development pipeline

The inclusion and exclusion criteria for the readiness cohort and the protocol for the connected proof of concept trial had been clearly defined at this point of the study. However, it remained unclear what these had changed *for* and what potential future treatment the drug trial was offering. One researcher described the situation as being "all a bit cloak and dagger at

the moment," given that the specific drug to be tested was yet to be revealed. Most people involved in coordinating the study and collecting data knew on *what* and in *whom* the drug was likely to act (i.e., on the protein "tau," in "prodromal" participants), but almost no one knew anything about the drug itself or to whom it belonged. The reason for this opacity was the uncertainty and precarity of the process of securing the drug with the intervention owner (the pharmaceutical company), which the future of the trial depended on. In fact, most of the study's leadership described the intervention not as one solid intervention package, but as a number of possible interventions "in the pipeline," with one intervention holding most promise for the future trial at any given time.

This uncertainty emerged from the project's position at one intersection of "precompetitive" and "competitive" space in drug development. Predicated on the creation of a platform through precompetitive collaboration, the ultimate operation of the platform depended on engagement with the "competitive" spaces of drug development. This was reflected in the difference between the transparent development of the platform and the opacity of the trial. Only a small and select number of people who had entered into nondisclosure agreements with potentially interested companies could "see into" the drug pipeline. Its contents had to remain secret until a final contract had been secured with the owner of the drug, with the wider consortium informed only that discussions were ongoing with a company about a drug at a particular stage and with a particular mode of action (e.g., an anti-amyloid drug currently at phase I). Although the project was a public–private partnership, the industry partners who were already involved were not necessarily those who would use the platform, with other, *external* intervention owners also able to buy in and start testing *their* compounds. This was delicate—a process one member of the study's executive committee described as "the intervention owner giving away their baby," going on to emphasize what a "valuable asset" a promising compound is to a company. And so, while the readiness of participant bodies and brains was constantly being measured and made *visible*, the (non)readiness of the drug was being kept largely *in*visible.

The drug as absence: An "ontology of withdrawal"

While the drug was described in some conversations as being invisible, in others, it was talked about as being manifestly absent (Law 2004):

> Oh [the readiness cohort] is a great idea! But we need a drug now. Today. We need a drug two years ago.

This came from an industry partner, whose involvement in a number of other clinical trials made her skeptical about whether the *trial platform* was "ready" to enter into the next phase of drug testing. As described above, the commitment of the IMI and its industry partners was to create a shared framework for potentially competing actors to conduct simultaneous trials. Understandably, therefore, this partner was concerned about the lack of a drug itself at this crucial point in the study. After all the discussion about a particular drug determining the readiness of participants, this drug became evanescent when it came to operationalizing it in the trial itself. Even more curiously, many of our interviewees and participants in the meeting accepted this absence and maintained that the drug trial was ready to go ahead. In contrast, for another senior data scientist involved in the trial platform:

> . . . the first goal of EPAD is to deliver a clinical trial: The proof-of-concept trial. So, is EPAD ready for that? I think, *absolutely.*

These answers were not the only diametrically opposed responses to our question about the "readiness" of the trial platform itself, there was little agreement on this among our interviewees. After so much protocol adjustment to achieve agreement about participant readiness, this disagreement about the implication of the absent drug was striking.

Unlike the modeled trajectory of cognitive and biological decline that provides its basic logic, the trajectory of drug development itself emerged as unpredictable and nonlinear. In narratives about the readiness of trial platform, the potentiality of the drug was less about an innate potential of the compound and more about the potential of what *might be*, but is *not yet there*. This is the "complex work" of potentiality: "to imagine or talk about potential is to imagine or talk about that which does *not (yet and may never) exist*" (Taussig, Hoeyer, and Helmreich 2013, S4). Indeed, at the time of our research, the *absence* of the drug was what held the potential to do what previous drug trials had repeatedly failed to do: work on earlier-than-ever stages of the disease trajectory to stop cognitive decline.

This future orientation speaks also to the notion of *speculation*, the practice of casting into an unknown future from a known present. The opaque "cloak and dagger" of the drug pipeline animates Bryant and Knight's (2019, 83) conjecture that speculation is where the "weirdness

of the world" and "our inability to pin it down" leads to imaginative knowledge practices. Our attempts to follow the drug in our interviews, only to find it vanishing from view, echo what Bryant and Knight call the "ontology of withdrawal": of things disappearing or not making themselves known as we inhabit the speculative gap.

Working in the speculative gap (or, the intervention's new clothes)

In this paper, we have opened up the sociotechnical "black box" of the readiness cohort, attending to what was present, what was absent, and what was "not yet" in this particular case study. Crucial to this has been exposing how the drug operated as a "not yet"—something which has taken on renewed meaning as we reflect upon the trajectory of the trial platform now that the project has drawn to a close. In fact, the intervention never arrived: no trial was launched, and no drug was tested. The drug was (and remains) a speculative, anticipatory entity, but no less powerful for it. The speculative promise of the drug could not be taken away, because, on the one hand, so much depended on it, and on the other, it did not (yet) exist. As Gibbon (2013) has observed in the field of cancer genetics, science does not hold innate potential but rather is imbued with it via various local articulations of knowledge and technology. We can describe the drug as a powerful but ambiguous placeholder in this study context: a placeholder around which progress in drug development and testing are able to "happen" in various ways in response to changing articulations of knowledge and technology. Where does this leave our concept of readiness, dependent as it is on this unreliable object?

Readiness, as an analytic as well as the condition we have been describing empirically, is characterized by its *workability*—its contingency on moving parts and changing thresholds in a scientific project being put into practice. It remains highly pragmatic, as well as fluid, in the context of the trial platform. Its parameters and thresholds respond to the changing availability of potential drugs as well as the changing definitions of potential (preclinical or prodromal) Alzheimer's disease. Here, we are reminded of Clarke and Fujimura's "Right Tools for the Job" in which all these components (tools, jobs, and "rightness") are situational and contingent; and how specifically, "designations of the 'rightness' of timing . . . is circumstantial" (Clark and Fujimura 1992, 5).

The construction and maintenance of a readiness cohort *appeared* to be full of linear movement toward disease modification or cure, seeking to stay "one step ahead" of the disease trajectory itself. But what we learn from the

operationalization of readiness is that trajectories of disease development and pharmaceutical drug development are meticulously *coordinated* in a forward-moving path, with the setting of readiness-thresholds being a key part of this coordination. Attending to this tells us that the linearity of the "readiness" story is constructed rather than natural (a now well-rehearsed line of argument in Science and Technology Studies [STS]), but it also highlights how specific threshold-setting is both defined by drug development imperatives *and* what makes drug development work. Making drug development work, in turn, makes a definition of Alzheimer's disease as a linear progression work. This observation speaks to other ethnographic accounts of clinical trials and how their "therapeutic regimes" shape the diseases that are their research objects (Cambrosio, Keating, and Nelson 2014). Readiness remains temporally defined and bound to the bodily and cognitive change associated with dementia, but its specificity is shaped by many other dynamic forces: material, political, financial, and scientific.

The need for temporal specificity is tightly bound to the story of "reengineering" Alzheimer's research, which we outlined in the introduction. The public–private partnership was deeply invested in developing drugs that showed an effect on cognitive decline, even as the focus shifted to earlier, less detectable stages of the disease. The promise of such partnerships is to enable companies to collaborate with each other and with public-sector partners in a "precompetitive" way that "de-risks" pharma research (Laverty and Meulien 2019). However, the process of establishing readiness brings to the fore the balancing act involved in such efforts, between a *clinico-scientific* logic of "earlier the better," a *commercial* imperative not to test drugs "so early" that effects would not be captured on regulator-approved measures, and a funding and regulatory framework that attempts to create a space for collaboration within a competitive industry. The self-described "neutrality" of this collaborative platform (Laverty and Meulien 2019) was not about being intrinsically disinterested (financially or scientifically), but rather the balance this act *sought* to achieve.

Conclusions

In this paper, we have followed our expert interlocutors' definitions and enactments of the temporal state of readiness. We have analyzed the threshold for becoming trial-ready in terms of its temporal specificity: the *right moment* for the *right individual* to respond *optimally* to a given drug. We argue that this specific threshold is not only determined by the biologies and psychologies of individual cohort participants, it is also a more distributed

achievement, involving other actors and materials such as intervention owners and the trial infrastructure itself. This makes space for a sociopolitical analysis of "the timing" of drug treatments and trials in Alzheimer's disease and more broadly. Pushing this argument further, our empirical material shows how readiness is also contingent on things that are absent, or "not yet," such as the drug yet to be tested within the trial platform.

Our approach shines a light on absent entities that nevertheless hold power and potential; something we suggest opens up possibilities for a *speculative ethics* in this field (Puig de La Bellacasa 2017). In this way, we have exposed how thresholds relating to biological trajectories of cognitive decline had to be adjusted and aligned to the uncertain trajectories of drug development. The invocation of "not yet" when it comes to both the development of symptoms *and* the drug that will eventually treat these symptoms reinforces the entangled forward-moving trajectory of cognitive decline and drug development: the race to "beat the biological clock." In loosening, denaturalizing, and questioning the logics of the linear progression of these trajectories, we might think about future potential not just in terms of "not yet" but as "otherwise" (McTighe and Raschig 2019).

This "not yet" or "otherwise" question relates to the problem–solution space of Alzheimer's disease. We have demonstrated that decisions about readiness were in thrall to a drug that did not yet and may never exist. The absent drug was a placeholder for the changing needs, goals, and politics of disease modeling and drug development: the speculative gap between problems and solutions. This analysis of readiness echoes Brown's (2000) description of the "breakthrough motif," as "intrinsically tied to the twofold practical orchestration of present problems and future solutions" (p. 89). But unlike the rhetorical breakthrough motif, readiness *enacts* and *performs* both problems (the pre-Alzheimer's trajectory) and solutions (drug development). In other words, readiness makes both the predisease trajectory and drug development *plausible* and *workable* in an uncertain clinical trial context.

It is here that we might engage with the "politics of the (im)possible" (Wilkie, Savransky, and Rosengarten 2017) and consider what *else* might be plausible and workable in the bigger picture of Alzheimer's disease prevention. By highlighting the genuine openness of the question "ready for what, and at what time?" we discover an emerging opportunity to participate in a conversation about what, exactly, holds potential in the field of Alzheimer's disease prevention. Our contribution has told the story of the absent drug that was part of a distributed set of entities that set thresholds for trial readiness. But what if we considered entities that were not just

absent but completely invisible or other when it comes to the world of clinical trials (Law 2004)? This includes the much broader assemblage of people, things, and tools missing from this particular story, which was shaped by the core group of scientific actors we described in our introduction to the EPAD case. Critical historical accounts have highlighted alternative paths, which have been neglected or even "thwarted" in the broader story of Alzheimer's research (Begley 2019; Lock 2013, 67, 215; Ballenger 2006, 81). Given the contingencies we have pointed out in this paper, the "right time" for the "right sort of participant" to receive the "right intervention" may look very different if we were to open up the speculative gaps enough to include other scientific actors, different (un)willing bodies, and neglected things (Puig de la Bellacasa 2010) within the field of Alzheimer's research.

Arriving at such a conclusion gives us pause for thought about the limits and possibilities of our project, "awkwardly suspended" between observation and collaboration with clinical research (Balmer et al. 2018). Does this collaborative project afford the kind of risky suggestions or "outrageous propositions" (Greco 2017) that speculative social research incites us to make? Can we *participate* in the speculative work of adaptive clinical trials, while maintaining our critical stance on the opacity of the drug development process? Without claiming to have answered these questions, we treat this as an opportunity to orient ourselves toward the speculative. As researchers, we can propose alternative ways of thinking about the politics of time and timing, brains, and biology as we approach the uncertain future of Alzheimer's disease research. And as participants in this collaborative work, we seek to highlight the speculative space and facilitate openings for a broader constituency of actors to occupy this space. In both cases, we call for a more generous set of engagements with timings, timescales, and techno-futures done "otherwise" as we move through the speculative gaps of neurodegenerative disease and its prevention.

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Note

1. At the time, the most recent failure in a string of pharmaceutical drug trials, this one being a compound targeting beta-amyloid tested on participants with prodromal Alzheimer's disease, much like the trial European Prevention of Alzheimer's Dementia was gearing up to implement. At the time of writing, aducanumab has been resurrected as a potentially "successful" drug and is being submitted by Biogen for Food and Drug Administration approval.

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