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Testing devices or experimental systems? Cancer clinical trials take the genomic turn

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ABSTRACT

Clinical trials are often described as machine-like systems for generating specific information concerning drug safety and efficacy, and are understood as a component of the industrial drug development processes. This paper argues that contemporary clinical trials in oncology are not reducible to mere drug testing. Drawing on ethnographic fieldwork and interviews with researchers in the field of oncology from 2010 to 2013, we introduce a conceptual contrast between trials as *testing machines* and trials as *clinical experimental systems* to draw attention to the ways trials are increasingly being used to ask open-ended scientific questions. When viewed as testing machines, clinical trials are seen as a means to produce answers to straightforward questions and deviations from the protocol are seen as bugs in the system; but practitioners can also treat trials as clinical experimental systems to investigate as yet undefined problems and where heterogeneity becomes a means to produce novel biological or clinical insights. The rise of "biomarker-driven" clinical trials in oncology, which link measurable biological characteristics such as genetic mutations to clinical features such as a patient's response to a particular drug, exemplifies a trend towards more experimental styles of clinical work. These transformations are congruent with changes in the institutional structure of clinical research in oncology, including a movement towards more flexible, networked research arrangements, and towards using individual patients as model systems for asking biological questions.

1. Introduction

As the "gold standard" of contemporary evidence-based medicine, clinical trials have attracted attention from both social and biomedical scientists (e.g., Timmermans and Berg, 2003). In this paper, we examine assumptions about how clinical trials should function, their aims, and the knowledge they should produce. One common way of conceptualizing the function and aims of clinical trials—that they operate like an industrial drug testing process—has deep roots that extend back to the early days of clinical research in oncology. In the United States, the Cancer Chemotherapy Program developed in the mid-1950s was initially inspired by wartime successes with government-funded antimalarial and antibiotic development programs. The program was designed to join large-scale animal screening efforts with evaluation in human clinical trials to create a centralized and sequential model for anticancer drug development (although it quickly evolved into a more distributed form of research, performed by a network of "cooperative groups"; Keating and Cambrosio, 2011). This view of clinical trials as drug testing machines continues to be more than just a metaphor. The Clinical and Translational Science Award (CTSA) Consortium, for example, aims to develop a "virtual laboratory" for reengineering clinical research by employing techniques used to evaluate and increase efficiency in other industrial processes, such as the automobile and semiconductor industries (Dilts et al., 2012). Heirs to the "Cold-War rationality" approaches analyzed by Erickson et al. (2013), the conceptual models of the drug development process employed by this initiative are highly schematic, representing clinical trials in terms of process flow maps and sequences of decisions that can be used to pinpoint regulatory or decision-making barriers and optimize the system.

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Social science analyses of clinical trials often implicitly reinforce this testing machine view by portraying clinical trial protocols as a means to enforce rules, to discipline the conduct of human subjects, and to increase market share (Abadie, 2010; Berg, 1998; Fisher, 2009; Petryna, 2009). These approaches emphasize the relative lack of agency experienced by both study subjects and contract physicians in the face of fixed and inflexible clinical trial protocols. Other sociologists treat clinical trial protocols as a site of social negotiation where the interests of patient groups, health professionals, drug developers, and regulators intersect (Greene, 2007; Marks, 1997; Will and Moreira, 2010). While challenging the notion that clinical trials act as straightforward expressions of corporate agendas or administrative exercises, these interpretive strategies do not directly address the capacity of trials to generate new knowledge or to suggest new questions beyond the safety and efficacy of new drugs.

There is a growing sense in both the social and biomedical science communities that we are presently observing fundamental shifts in the practice of clinical research in oncology; shifts that call for new theoretical frameworks for understanding these changing aims and epistemic orientations. If clinical trials are often described as testing machines, then clinical trialists today speak of them as decrepit ones that are too slow, unwieldy, and uneconomical for an era that demands flexibility and fast results. Discussions about the current state of drug development often follow a familiar narrative about a crisis of productivity: pharmaceutical companies are investing record amounts of money in research and development, while at the same time the number of new drugs approved by the FDA annually has declined since the 1990s (e.g., Esserman and Woodcock, 2011). In oncology, the problem is particularly acute. Nearly 95% of new oncology drugs entering the clinical trials system fail to reach approval, often failing only after they have reached the expensive Phase III stage (Kola and Landis, 2004). With hundreds of new agents in the pipeline waiting to be tested (Pharmaceutical Research and Manufacturers of America, 2009), the long lag between the design of a study and the enrollment of the first patients has led some prominent clinician-researchers to argue that "the clinical trials system is broken" (DeVita, 2008) and in need of a "radical overhaul" (Kirk and Hutchinson, 2012).

These critics argue that the current one-size-fits-all approach to drug development is especially ill-suited to deal with a new generation of anti-cancer agents that are targeted at specific molecules or mutations (Kirk and Hutchinson, 2012), and it is here that proposals to streamline the trials system with industry-inspired operational efficiency approaches intersect with new "biomarker-driven" trial designs. These new designs aim to speed up the movement of drugs through the metaphorical "pipeline" from bench to bedside by linking measurable biological characteristics, such as gene expression or genetic mutations, to clinical features, such as a patient's intrinsic potential for response to a particular drug. Proponents argue that using biology to reform clinical trial design will make drug testing more efficient by selecting patients who are likely to respond to the drug from those who are not, rather than relying solely on the power of large numbers to make a drug's efficacy visible. But these reforms are about more than just efficiency: Members of the UK-based Institute of Cancer Research have hailed biomarker-driven trial design as a "paradigm shift" that will allow drug developers to realize the promise of personalized medicine (Tan et al., 2009). Leaders of the European TRANSBIG consortium (a clinical research network promoting individualized treatment in breast cancer) have similarly argued that these biology-focused trials represent a programmatic shift in clinical research from an "empirical" approach that tests the efficacy of one treatment versus another to a "tailored" approach that asks biological questions (Fieldnotes, 8ème Biennale de cancérologie, Monaco, January 2008).

These recent trends towards designing targeted, biomarker-driven, or biopsy-driven trials have intensified the connections between clinical research and scientific experimentation. While clinical research in oncology has arguably always been an epistemic activity that exceeds mere empirical testing of anti-cancer therapies (Keating and Cambrosio, 2011), these new trial designs greatly expand the extent to which clinical trials are a site for investigating questions about disease biology. Existing modes of describing drug development in oncology—such as the aforementioned, ubiquitous "pipeline" metaphor—obscure the surplus of activity and knowledge production within clinical trials that is not reducible to mere drug testing, and thereby simultaneously obscure the significance of these shifts towards a more biology-driven style of clinical research by reducing them to a series of organizational or technical issues that slow down or speed up the "flow" of drugs through the system.

In this paper, we develop the notion of trials as *clinical experimental systems* and contrast it with a view of trials as *testing machines*. While understanding clinical trials as empirical machines designed to answer questions about the safety and efficacy of new therapeutics is a familiar way of conceptualizing clinical research practices, we demonstrate some of the ways in which scientific actors also treat clinical trials as devices for materializing new questions about cancer biology and treatment. The trend towards biomarker-driven clinical trials, with their biological hypotheses and numerous ancillary molecular studies, has made this viewpoint much more apparent. Indeed, these new trials share many of the characteristics of experimental work that historian and molecular biologist Hans-Jörg Rheinberger (1997) describes; such as the capacity to generate surprises, the interplay between continuities and discontinuities with prior lines of research, and the need to keep some objects stabilized while opening others up for investigation. We outline four aspects in which the clinical experimental systems view differs from the trial machine view: the management of heterogeneity, the flexibility of protocols, the institutions needed to execute the trials, and type of information that can be gleaned from clinical trial participants. Contrasting these two ideal-typical ways of conceptualizing the clinical trial provides a vocabulary that is particularly useful for understanding the tensions surrounding the implementation of hybrid trial designs and new research practices that attempt to satisfy both experimental and testing aims, and for understanding the increasingly dense connections between the laboratory and the clinic that are prominent in emerging forms of translational research.

2. Methodology

Our argument is developed out of fieldwork conducted in a recently established Canadian clinical oncology research consortium called the Quebec Clinical Research Organization in Cancer (Q-CROC). Created in 2009, one of the aims of the Q-CROC network is to develop scientific and clinical expertise around the problem of resistance to anti-cancer therapies. We closely followed a clinical trial (Q-CROC-03) that examined resistance to treatment in patients with a particularly difficult to treat form of breast cancer known as "triple-negative" breast cancer (TNBC). This trial offered a valuable site for studying new forms of clinical research practice because it was a hybrid of biologically intensive laboratory techniques and traditional clinical research practices. Rather than testing a new drug, the study aimed to discover new biomarkers for existing cancer therapies that might predict which patients would be likely to respond to those drugs using biological samples taken from the patients before and after therapy. The trial thus had the open-