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

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.

Keywords: Canada, clinical trials, drug development, oncology, experimental systems, biomarkers

Introduction

As the “gold standard” of contemporary evidence-based medicine, clinical trials have attracted attention from both social and biomedical scientists (e.g., Timmermans & 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 & Cambrosio, 2012). 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.

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 & 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 & 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 & 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 & 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 & 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 & Cambrosio, 2012), 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.

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-ended discovery goals of a basic science endeavor, but was executed using much of the same infrastructure—institutional review boards (IRB), clinical research coordinators, participant recruitment venues, specialized patient beds and procedure rooms—developed for trials testing the safety and efficacy of novel therapeutics.

The first three authors of this paper are social scientists, while the last two are biomedical scientists who designed and executed the Q-CROC-03 clinical trial. At the grant application stage, the two trialists invited their social science colleagues to join the team as members of the GE³LS (genomics and its ethical, environmental, economic, legal and social aspects) component of the trial to investigate the reconfiguration of clinical research in the genomic era. Following successful peer review of the proposal, the social scientists had extensive access to the Q-CROC-03 trial as co-investigators, including access to planning meetings, visits to the opening of new study sites and the monitoring of the data collected, ongoing email correspondence between the coordinators and the sites, sample processing practices, laboratory meetings discussing scientific results,

meetings with funding agencies, the annual meeting of the Q-CROC network, and the network's intranet. The material for this paper thus comes from truly participant-observation (or "embedded-observation") over a three year period.

We collected several types of data, including observational fieldnotes, semi-structured interviews, and documents from the clinical trial. The social scientists observed 41 independent trial events such as site initiation visits, monitoring visits, team meetings, data analysis meetings, conference presentations, and sample preparation work. Fieldnotes were recorded during these events and later compiled into fieldwork memos that were circulated amongst the research team members. These field notes were supplemented with semi-structured interviews with five Q-CROC team members, who were selected for their central involvement in the clinical trial and the Q-CROC network (7 interviews total, averaging 71 minutes in length). These interviews, which took place on location at the hospital, focused on collecting more background and detail on issues that arose during fieldwork, and they were audio-recorded and transcribed in full. The observational fieldnotes, interview transcripts, and other materials collected throughout the course of the trial were coded by the social scientists for recurring themes using standard qualitative data analysis methods (e.g., Saldaña 2009) to develop empirically grounded frameworks for thinking about clinical research. Preliminary findings were shared with the clinical authors for feedback as the frameworks were developed.

"Embeddedness" in an ethnographic field site requires a balance between direct involvement and critical distance, the latter being supported in this case by the fact that

separate funding sources allowed the social scientists to conduct additional independent investigations on cancer genomics at other sites. Thus, in addition to the Q-CROC ethnographic fieldwork, this paper incorporates data from interviews with lead investigators in other clinical trials in the United States and Europe, observations gathered from international oncology meetings, and the published literature in oncology. The additional trials and sites selected were part of a broader project on cancer genomics, and interviewees were selected for their central involvement in high-profile trials that promote biomarker-driven clinical trials approaches (98 interviews in total with 87 unique interviewees, averaging 73 minutes in length and ranging from 17 minutes to 143 minutes). Interview sites included the Memorial Sloan Kettering Cancer Center, one of the preeminent cancer centers in the world; clinical researchers involved with the BATTLE trial, one of the first oncology clinical trials to use biomarkers to assign patients to treatment, at the similarly preeminent MD Anderson and elsewhere; researchers in the I-SPY 2 consortium, a U.S. group that has a large and ongoing study that also uses tumor biomarkers to direct patients' treatment; and, on the European side, trialists from the POETIC trial in the UK, which sampled breast cancer patients' tumors before and after therapy (like the Q-CROC-03 trial) with the aim of developing new biomarkers to personalize patients' treatment plans, and from the SAFIR trial, sponsored by the French network of comprehensive cancer centers. The data collected from these interviews were analyzed as described above and compared to the ethnographic material collected in the Q-CROC consortium to refine the emerging theoretical frameworks. These two sets of data are also complementary in that the ethnographic fieldwork provided us with an understanding of the day-to-day reality of biology-driven clinical trials, and the

interviews and observations of other prominent trials allowed us to relate these local observations to broader trends in the field.

Literature review and conceptual framework: Trials as clinical experimental systems

José Baselga, the recently appointed Physician-in-Chief of the Memorial Sloan Kettering Cancer Center in New York City, describes himself as a “drug developer” with a mission to reform the MSKCC’s clinical research program around a more “mechanistic-based approach” (see also Buettner et al., 2013). Rather than simply screening drugs offered to them by pharmaceutical companies, he and his team seek to understand the molecular pathways driving cancer development, proactively contact pharmaceutical companies with drugs inhibiting certain pathways, and then move interesting drugs into clinical trials. Their process, as he describes it, consists of “taking a [molecular] inhibitor, talking to the guys in the lab, [and asking] what are the markers of dependency [on this pathway molecule]? Can we create a signature in tumors that is predictive of [this molecular] dependency? Can we interfere? It’s an experiment!” (Interview May 16, 2013).

“It’s an experiment!” But what does it mean to characterize this work as experimental? In recent social science work on the role and nature of clinical trials it has become increasingly common for analysts to describe trials as experiments. The term is sometimes used in a literal sense, as when Brives (2013, p. 399) argues that “trials are essentially scientific experiments”, and sometimes in a metaphorical sense, as when Will

and Moreira (2010) describe them as “social experiments.” Petryna’s (2009) characterization of global pharmaceutical trials under the rubric of “experimentality” lies between these two poles, as she uses the term to critique experimentation on human subjects while drawing attention to the uncertain social consequences of the expansion of clinical trials and their capacity to “redistribute public health resources and occasion new and often tense medical and social fields” (Petryna, 2009, p. 30). Cooper (2012), using a notion of experimentation that shares much in common with our own, argues that new forms of clinical research designed to rethink translational medicine have introduced an element of “experimental surprise” into contemporary clinical research. Rather than exploring the consequences of these developments for translational research, as we do here, she focuses on “post-Fordist” forms of labor associated with distributed forms of clinical research such as social networking platforms for collecting patient data.

Analysts have also noted the capacity of clinical trials to generate knowledge beyond findings about the safety and efficacy of new therapeutic compounds. Kimmelman (2012), for example, argues that early phase research also acts as a site assembling what he terms the “intervention ensemble”—the suite of technologies and practices that when used together with a drug will unlock its therapeutic potential. Will and Moreira (2010) argue more generally that clinical trials act as a site for generating new entities and relationships between entities, such as the iterative relationship between drugs and disease entities that Vos (1991) explored in his pioneering study of the development of anti-hypertensive compounds. Keating and Cambrosio (2012) have similarly shown that

clinical trials have historically provided an important site for oncologists to elaborate and reform their notions of cancer biology.

In this paper we develop a more analytical sense of clinical trials as experiments that generate new entities, drawing on the notion of *experimental system* articulated by Hans-Jörg Rheinberger (1997). Rheinberger argues that the defining characteristic of experimental work is its capacity to act as a “generator of surprises” (1997, p. 3). What makes something an experiment, as opposed to a test, is its ability to generate unprecedented and unanticipated events, rather than simply providing predefined answers to standard or routine questions. Baselga provides us with an example of such a “surprise” from a recent clinical trial leading to a new line of clinical work:

You do sequencing, and then you begin to see things that are fascinating ... I look at the samples and I find out that 29% of the samples [from a recent study] have mutations of the estrogen receptor. If you look at [published data, the rate] is 7%. So now you have a sample set that under selective pressure goes from 7% to 29%, and the majority of these mutations are functional. So I mean, hello! ... The message is very clear. ... I see this data. What do I do? I immediately call every single company and ask, how are we going to attack this [mutated receptor]? How are we going to attack this thing?

This is not to say that the findings produced by experimental work are entirely novel or unrelated to previous results—if they were, there would be no framework for

understanding them. Rather, the results generated by a series of experiments can be thought of as “pieces that fit or do not fit into an ongoing puzzle” (Rheinberger, 1997, p. 80). Rheinberger accounts for this tension between continuity and discontinuity in experimental work by describing experimental systems as comprised of two types of objects: epistemic objects, whose contours and responses to experimental manipulation are the target of investigation, and technical objects, which act as “answering machines”. The properties of technical objects are specified in advance, and they serve as the sociotechnical space within which the epistemic objects are deployed, questioned, and represented. Both technical and epistemic objects are defined in functional and context-dependent as opposed to ontological terms. Today’s object of inquiry may become a technical object for running future experiments, and regain the status of an epistemic object in a new topical contexture (Lynch, 1991).

Attentive readers will have noticed that we speak in this paper of *clinical* experimental systems rather than simply experimental systems. The clinical nature of the work that we are studying differs from laboratory work in a number of important ways. Clinical trials are collective, often globally distributed activities that cannot be contained within a single laboratory or directed by a single investigator. The heterogeneity of clinical trial collectives has implications for how objects become stabilized as technical objects or opened up as objects of epistemic inquiry. This heterogeneity refers to both the presence of different professional groups and to the dual clinical-biological nature of its biomedical components. The focus of the Q-CROC-03 trial—TNBC patients—provides an excellent example of the bioclinical nature of certain objects within clinical

experimental systems. The three negatives in TNBC refer to the absence of three different cellular receptors. This designation has both biological and clinical significance: their absence means that patients cannot be treated with therapies that target those receptors, but it also represents a biologically distinct (although controversial) subclass of breast cancer (Keating et al., 2013). For the purposes of the trial it is held fixed as a technical object to define enrollment criteria, but the trial itself may well lead to results that destabilize either the biological or clinical significance of the category. Moreover, stabilizing this category for the purposes of the Q-CROC trial was challenging due to different definitions of “negative”: some pathologists defined a tumor as negative if less than 1% of the cells expressed the receptor, while medical oncologists often used a 10% threshold for the purposes of treatment.

[Table 1 approximately here]

Table 1 summarizes the main features of the two contrasting views of clinical trials as testing machines or as clinical experimental systems, which are explored in greater depth in the remainder of the paper. While the machine view sees the main purpose of clinical trials as generating a yes-or-no answer to the question of whether a new therapy is superior to existing therapies, the experimental systems view sees the clinical trial as opening a space for asking open-ended questions. The goal of a clinical trial in the traditional view is to turn a messy clinical population into homogeneous units that can be compared, while experimental systems produce insights by managing heterogeneous,

“differentially reproduced” objects. Deviations from the protocol and unexpected results that fall outside of the specified questions asked are seen as bugs in the machine view, while in the experimental systems view glitches and departures from the expected are a feature of the system that allows for novel insights to emerge. In addition to these epistemic features, experimental work is also associated with particular kinds of institutional arrangements that are more flexible and ad hoc, as evidenced by the recent emergence of numerous public-private consortia groups and alterations to the longstanding cooperative group system. The favored experimental systems of clinical research—preclinical animal studies leading to small first-in-human studies, followed by larger trials—are also being supplemented with new experimental forms that use individual study participants as model systems for investigating bioclinical processes.

The contrasting descriptions of clinical trials as testing machines and clinical experimental systems that we present here should be thought of as ideal types or heuristics, not as a system of classification for actual clinical trials. Clinical trials as they exist in practice are likely to be hybrids that combine some aspects of each type, for instance acting as devices for generating answers to predetermined questions about new therapies while at the same time opening up a space for asking open-ended scientific questions and generating future inquiries. While the early-phase trials staged by Baselga’s team at the Memorial Sloan Kettering come quite close to a pure experimental form, many others, such as the I-SPY 2 breast cancer trial are better characterized as hybrids. Study leaders refer to the I-SPY 2 trial as an “engine” for rapidly evaluating investigational drugs and accelerating their approval (Esserman & Woodcock, 2011), but

to see the trial as merely a drug-testing machine is to miss the substantial departures that it makes from traditional empirical trials. The redesigned testing machine uses an “adaptive” design, whereby ongoing data from the clinical trial are fed back into the trial and used to modify its course in a way that, as one of the investigators puts it, allows researchers to “efficiently learn about something that is not completely established” (Berry, 2011, p. 200). Moreover, testing the efficacy of new drugs and aligning them with particular biological features of breast cancer tumors is only part of the work, for the trial is also producing information on new imaging technologies, investigational biomarkers for predicting responses to therapy, and biobanks of tissue that can be used for future research projects.

The distinction that we wish to draw is also historically specific and context-dependent, as the experimental form of clinical trials is linked to recent developments in cancer genomics and marks a transition from established ways of working in the field. We are not, however, arguing for an epochal transition from a purely empirical to a purely experimental situation: rather, we are articulating a distinction between different ways of understanding the purpose and aims clinical trials, a distinction that has become increasingly evident over time as molecular analysis techniques are more deeply incorporated into clinical research. As we will show, this distinction is not solely conceptual, but has practical consequences for designing, framing, managing, and regulating clinical trials.

Results

This section presents four themes resulting from our ethnographic fieldwork, which highlight the contrast between these two ways of viewing the aims, functioning, and outcomes of clinical trials. We discuss the significance of each theme in turn, followed by a more general discussion in the last section on the implications of these findings.

Theme one: Homogeneity versus productive difference

The first theme arising from fieldwork in the Q-CROC-03 trial was a recurring tension between creating a homogeneous set of clinical data and capitalizing on differences between patients, samples, or techniques. The analysis of samples in the Q-CROC trial demonstrates these two different modes of dealing with the differences that inevitably arise in the course of clinical trials. Tissue samples were collected from patients at several different times (before chemotherapy treatment, after treatment, and at the time of surgery), using different methods (by freezing the tissue, preserving it in a specialized solution called *RNAlater*[®], or preserving it in formaldehyde), and with different qualitative outcomes (the biopsy needle might miss the tumor, resulting in a sample containing mostly normal tissue, or the tumor tissue collected might be necrotic and therefore unusable). These variables meant that matched pairs of samples had to be created for a comparative analysis, since it was rare to find two pre- and post-treatment samples from the same patient that did not differ in some more or less relevant way.

In some instances, the Q-CROC team dealt with this variation by treating some differences as irrelevant. A frozen pre-treatment sample might be paired with an

RNA*later*[®] post-treatment sample, thus minimizing and erasing difference to bring samples back into line with the testing machine ideal of samples that only differ in one important aspect (the treatment or intervention). In this understanding of clinical trials, management techniques here serve to minimize departures from the protocol and to reduce the number of samples that fail “quality control.” As Helgesson’s (2010) ethnographic study of clinical trial data managers similarly shows, clinical trial practitioners use a number of formal and informal practices to contain the numerous small deviations that arise during the course of a trial to create an “aligned and consistent” set of data, thus increasing the perceived credibility of the trial. Differences are ideally highly constrained and deviations are treated as unavoidable but undesirable sources of error.

In other cases, the team shifted focus from the production of homogeneity to the exploration of the potential value of differences for generating new insights and biological hypotheses. One extended discussion dealt with a set of samples that were collected from a patient’s lymph nodes at the time of surgery. The collection of these samples represented a departure from the protocol (which called for primary tumor biopsies only), and they differed from the other tumor biopsies in that lymph node samples tend to have low tumor density and high numbers of lymphocytes. Rather than excluding the samples, however, the PI suggested using flow-sorting techniques to isolate different cell populations, with the hope of generating a methodological paper on the application of flow sorting to clinical samples and thus producing a “nice story” about the heterogeneity of tumor tissues (Fieldnotes, February 2012). After sorting and analyzing

the cell populations, the team found that only a very small proportion of cells in the lymph node tissue showed genomic abnormalities, a surprising outcome given the aggressive clinical history of this patient's tumor. This unexpected finding generated further discussion about how these findings might compare to data from the primary tumor samples, and hypotheses about how this small population of cells might control the aggressive clinical behavior of the tumor. At the conclusion of a lab meeting discussing these results, the study coordinator shared a motivational cartoon whose caption nicely captured the sense of the shift from regarding the lymph node samples as simply a failure to meet collection guidelines to seeing them as the starting point for an interesting scientific story: "What you think are insurmountable problems are just unlimited opportunities in disguise!" (Fieldnotes, September 2012).

This example shows not only how deviations can become a productive source of insights, but also how the epistemic value of tissue samples is not firmly fixed by a trial protocol and may change over time. This orientation towards as yet unknown questions and problems characterizes experimental systems as "machines for making the future" (Jacob, 1988, p. 9; see also Rheinberger, 1997, p. 28) and is often evidenced in biomarker-driven clinical trials through the collection of tissue samples as a resource for future knowledge production. In the Q-CROC trial, the primary objective of identifying biomarkers correlated with treatment resistance is supplemented by the secondary objective of creating a biobank of blood and tumor samples for future research (Basik et al., 2013; Diaz et al., 2013). The Q-CROC researchers have already used the banked blood samples as the basis for a new research project (and a new grant proposal) on blood biomarkers.

Similarly, one of the lead investigators of the BATTLE trial, a study that used tumor biomarkers to direct treatment for lung cancer patients, has urged researchers to collect as much tissue from patients as they can because one of the main benefits of such a trial is that it can be used as a “discovery platform” for testing findings from basic research in clinical samples (Fieldnotes, March 2012 Q-CROC meeting). The European TRANSBIG consortium has defended their MINDACT trial, which has been critiqued by some as an expensive answer to a simple question, on the grounds that it will create a high-quality biobank of tissues collected under ideal conditions for future research: as one researcher put it, “tissue is the issue” (Fieldnotes, IMPAKT 2012). The development of tissue biobanks is a way for researchers to establish an experimental space in which to ask new bioclinical research questions.

Theme two: fixed protocols versus evolving plans

Another recurrent theme in the Q-CROC-03 trial was a conflict between the need to formalize plans of action for the purposes of running the trial and the desire to adapt plans to new technologies or findings. Initially the trial was designed so that study patients would have samples of their tumor collected using a biopsy needle before they started chemotherapy treatment, with a second sample collected at the time of the surgery. A few months into the study, however, the principal investigator (PI) attended a workshop at the National Institutes of Health (NIH), where new data showed that the gene expression profiles of samples collected at the time of surgery were substantially

different from biopsy samples (Interview May 31, 2011). After seeing these data, the PI became concerned that their protocol would not yield high-quality biomarker information because of the noise caused by this difference (Fieldnotes, April 2011). Weeks before their first study patient was due to have her surgery, the team decided to amend the protocol to provide for a second sample to be taken using a biopsy needle a few days before surgery. Similar problems arose around the techniques used to collect and store tumor samples when preliminary data showed that the original technique yielded mixed results on downstream analysis platforms, leading to another set of protocol changes.

The Q-CROC team's choice to adapt their protocols rather than staying with the protocol as written did not always sit easily within the existing clinical trials infrastructure. While the experimental system acts as a "labyrinth" that both guides researchers and blinds them to what might come next (Rheinberger, 1997, p. 74), the pre-specified protocol occupies a central role in coordinating practices and defining relationships between the various actors and objects involved in the clinical trial as testing machine. The aforementioned changes to the biopsy protocol in the Q-CROC-03 study necessitated a series of amendments that had to be approved by the IRBs of each local hospital. This generated an enormous amount of labor for the study coordinator and created tensions with some of the participating hospitals. In one case, the additional work required by the amendments was enough to cause one local site to threaten to withdraw a year into the study:

Fieldnotes, January 2012: The study coordinator called a local hospital to check up on the status of the amendment for the second biopsy and was told that they had just discussed the Q-CROC study at a morning meeting and had decided to close it. The PI quickly got on the phone to the local investigator to try to change his mind before he closed the site officially. The local investigator told him that the amendments and the second biopsy were just making the study too complicated, and that they wanted to focus on studies that were easier to run.

In the end, the local hospital agreed to continue participation only if they could run the study as originally designed without the protocol changes at their site, a compromise that the PI was willing to make to obtain research samples.

Attempting to manage a clinical trial like an experimental system from within a framework of institutions (such as IRBs) and practices (such as those of local clinical research staff) that expect clinical trials to function like machines with fixed plans may be why biomarker studies are frequently described by trialists as complicated to run. Other biomarker trials have also encountered problems with stabilizing bioclinical objects and routines enough to make a trial feasible while maintaining the openness that allows unanticipated results to emerge. The rapid pace of change in molecular biology techniques exacerbates these conflicts between stability and continuity on the one hand, and the desire to incorporate new knowledge and improved techniques on the other. In a report on the BATTLE trial, the study leaders observed that one of the main limitations of their trial design was that they pre-specified the groups of biomarkers used to assign

patients to different treatments (Kim et al., 2011). Over the course of the trial, they discovered that some of the biomarkers had little value and others would have been more useful for this purpose if they had not been grouped together, but they were unable to change the biomarker panel mid-trial. In the next iteration of the trial, BATTLE-2, they planned to address this limitation by “not grouping or pre-specifying biomarkers prior to initiating these biopsy-mandated trials” (Kim et al., 2011, p. 49); in other words, by introducing greater flexibility to allow new markers to emerge and old ones to be discarded, rather than simply testing the most promising markers available when the protocol is written. This strategy, in a sense, formalizes flexibility by explicitly building the capacity for mid-stream changes into the clinical trials machine.

Theme three: Stable institutions versus flexible networks

Another theme was the desire for greater flexibility not just at the level of local practices, but in the broader institutional arrangements for coordinating and executing clinical trials. In the United States, the cooperative groups have been at the core of clinical research in medical oncology since the 1960s. These public organizations, financed by the National Cancer Institute (NCI), act as a research platform to develop and conduct large-scale oncology trials in multi-institutional settings across the U.S., Canada, and Europe (Keating & Cambrosio, 2012). These organizations have recently come under sharp criticism in a report by the Institute of Medicine (2010) because of their alleged inability to adapt to the new era of targeted therapies.

Clinical research in oncology has also seen the recent emergence of numerous consortia, such as Q-CROC. These new networks are often public-private partnerships that involve both cancer research centers and pharmaceutical and technology companies, and in some cases are centered on particular research problems rather than the general business of running clinical trials. Q-CROC, for example, was designed around the idea of investigating the bioclinical question of resistance to cancer treatment. To this end, the network has developed expertise in taking multiple tumor samples from patients at different times during treatment. As one of the founders of the Q-CROC network noted, this required the development of new networks of expertise that included interventional radiologists, molecular pathologists, and core laboratories with advanced technology platforms (Interview March 21, 2013).

The experience of the Q-CROC researchers demonstrates how movements towards biology-based trials that require new forms of expertise have been driving organizational changes in the structure of clinical research. In the Q-CROC trial, the team recruited oncologists from one local hospital site who were active members of one longstanding cooperative group, the National Surgical Adjuvant Breast and Bowel Project (NSABP). They were surprised to find, however, that launching their biomarker study at this site was not as straightforward as they expected:

[This local hospital] is the vanguard of the NSABP in Canada, and so we went there thinking that [our study] is going to be like a knife through butter, it's going to be easy. That's their bread and butter so they do it all the time. And we're

stunned to find out that they couldn't get their [analysis of the molecular] receptors in on time, so it's a really big, big disaster. I actually had to go back to the [hospital] and meet their pathologist ... And I know somebody in the lab, a personal friend of mine works in the molecular pathology lab, and I phoned her. I said, "Listen, I need those receptors because we're ready to do something here." She says "I will get it for you in a week." This was five weeks ago (Interview May 31, 2011).

Even though these oncologists had extensive experience in conducting breast cancer clinical research through their involvement in the NSABP, the local hospital was not able to produce reports on the biological features of patients' tumors in time to identify patients with TNBC and enroll them in the study, and they did not have some of the necessary resources to collect fresh-frozen tumor tissue samples.

Trialists' desires for more flexible arrangements that can adapt to new trial designs are also driving institutional reorganizations. The I-SPY clinical trials, a set of studies aiming to accelerate the testing of new oncology drugs by using molecular and imaging markers, illustrates this shift. While the first I-SPY trial was conducted through the Cancer and Leukemia Group B (CALGB) cooperative group infrastructure, the second trial is sponsored by the Biomarkers Consortium, a public-private research partnership that includes the FDA, the Foundation for the NIH, major pharmaceutical companies, and non-profit and advocacy groups. Anna Barker, former deputy director of the NCI,

reflected that this move allowed them to bring together different streams of research and ask different questions than the cooperative group infrastructure was designed to support:

I-SPY 2 for me represented a convergence point for [a number of initiatives] ... knowledge of the biological systems, advanced technologies, new clinical trials models, et cetera. I saw I-SPY 2 as an opportunity to evaluate the best of what we knew in all of these areas; and an opportunity to bring that progress to patients in ways that would have been difficult to do through some of the other means that we support in the government. For example, the cooperative groups arose out of a need to do clinical trials for oncology drugs, as early in the history of oncology drug development no one else was going to do them. Over the years the cooperative groups came to do trials that often—but not always—represented incremental changes. In other words, a different regimen, a different dose, same drug, etc. As you might expect, given this focus and other limitations, rarely did these types of trials represent new models with the promise that we saw in the adaptive approach implemented in a consortia setting (Interview January 15, 2013).

In contrast to the cooperative group governance structure, the I-SPY 2 consortium arrangement allows for greater flexibility in how the trial is run, for example in changing over to new technology platforms as they become available.

The cooperative groups themselves have also quite recently undergone a series of rearrangements that extend beyond the recommendations of the 2010 Institute of Medicine report. The cooperative group system has been replaced by a new consolidated and integrated National Clinical Trials Network that supports new trial designs and collaborations, and allows academic centers to participate in multiple trials run by different network groups rather than having an affiliation with a single cooperative group (Printz, 2013). The recently activated “Master Protocol” lung cancer trial, for example, is coordinated by the Southwest Oncology Group but also involves the participation of other cooperative groups via the NCTN, the advocacy group Friends of Cancer Research, the Foundation for the National Institutes of Health and members of the FDA, pharmaceutical companies, and biotechnology companies (Ong, 2013). Such collaborations, which in many ways resemble the public-private networks pioneered by consortia groups, have led some practitioners to voice concerns about the future of the publicly funded NCI clinical trial infrastructure given the vital role it plays vis-à-vis industry sponsored cancer research (Schilsky, 2013)

Theme four: Participants as test populations versus participants as model systems

A final theme concerned changes in how clinical researchers framed and accounted for the role and the kinds of knowledge generated by clinical trial participants. Since the late 1990s, clinical trials have often been conceptualized as part of a translational research system that begins with so-called pre-clinical experimental work in cell lines and animals, and culminates with tests in human populations. While animal-to-human translational

work is still central to drug development, researchers frequently noted that new spaces of experimental inquiry are being opened up within clinical trials and even within trial participants themselves.

One of the Q-CROC founders argued that their work is distinct from other approaches because rather than modeling tumor response using animals or cell lines, they are measuring tumor response in actual cancer patients (Interview March 21, 2013). The design of the Q-CROC trials offers several opportunities for investigating biological processes by using the patient as an experimental system in which to study tumor response to treatments. The Q-CROC-03 trial, for example, uses a “neoadjuvant” study design that enrolls newly diagnosed patients scheduled to receive chemotherapy before surgery and takes samples of their tumor before and after the chemotherapy. Mitch Dowsett, one of the investigators in the British POETIC breast cancer trial that also uses a neoadjuvant design, describes his interest in the experimental potential of these new studies:

These scenarios are interesting to work in because you can get multiple tumor samples and you can look at the biological changes on those tumors; and in the tumor that you’re measuring in terms of its shrinkage, it did not receive previous treatment like an advanced disease situation. It’s a very clean biochemical situation we’re working with. I think people recognize now just how uniquely valuable this is (Interview with Mitch Dowsett, January 9, 2012).

Dowsett's description of neoadjuvant studies as a “clean biochemical situation” references the potential for these clinical trials to function as new spaces of experimental representation where bioclinical epistemic objects can be probed, investigated, and explored. Some researchers have argued that these studies offer a better experimental site for discovering and validating new biological markers than animal models (Interview with Laura van't Veer, November 27, 2012).

A similar but slightly more complex before-and-after study design is being used in Q-CROC trials, which focus on patients with advanced (“metastatic”) cancer. In patients with multiple tumors, these tumors may grow or shrink at different rates and new tumors may appear over the course of therapy, and investigators aim to track and biopsy these various tumors. As recalled by a Q-CROC investigator:

We had a patient that had metastatic colorectal cancer, multiple lesions, limited to the right lobular liver. And we got an initial biopsy of one of the most obvious tumors and started treatment ... So last Monday, he had a CT scan done three days before surgery, and what we found is that some of the tumors were smaller and stable, but some of them were obviously bigger and progressed on treatment. So in the operating room we had pictures of every single lesion, multiple biopsies of every single tumor—so we were going to be able to look at mixed responses, we were going to be able to look at tumor heterogeneity. It's a remarkable opportunity. (Interview with Gerald Batist, March 21, 2013)

Once again, the trial patient becomes a space in which scientific questions can be posed and experimental work can be done. Samples of the patient's multiple tumors (only some of which grew during chemotherapy) can be used to ask questions about the biological differences that make some tumors sensitive to chemotherapy and others resistant, or questions about how tumors evolve and begin to show biological differences over time. Moreover, the experimental objects investigated in the clinic are the same entities (mutations, genes) deployed in the laboratory: no mere analogy or metaphorical connections. As Baselga observed, "it's a moment of beautiful renaissance of the clinical investigator, because for the first time we are going to have tools that [will allow us] to learn from one [single] patient" (Interview, 16 May 2013).

Discussion: Implications of the tensions between contrasting views of clinical trials

As our presentation of the results has already suggested, the trial machine view and the clinical experimental systems view often point in different directions when it comes to making decisions about the execution of a clinical trial. Organizational structures such as the early cooperative groups, IRBs, and local clinical trial teams that are built on the assumption that protocols will largely remain fixed throughout the course of a trial can become sites of tension when trials are run in a more open-ended, experimental fashion. The contrast we draw between trials as testing machines and trials as clinical experimental systems resonates with longstanding rhetorical dichotomies between testing and discovery, or research versus application at issue in oncology more generally. In an

interview on the “state of the science” in oncology for the *GenomeWeb* newsletter, a researcher articulates this tension:

There are increasingly two schools of thought on cancer. One is that it is all an engineering problem. We have all the information we need; we just need to engineer the right drugs. The other school says it’s still a basic knowledge problem. I think more and more people think it’s just an engineering problem—give us the money and we’ll do it all. A lot of things can be done, but we still don’t have complete knowledge. (GenomeWeb, 2012)

The movement in oncology towards clinical trials that function more like experiments has intensified this longstanding tension in the field between a view that characterizes clinical trials as part of industrial drug development and a view that portrays them as bona fide research activities.

These conflicts between openness and stabilization, and discovery versus application, are evident in some of the disagreements that have arisen in Q-CROC team meetings. One suggestion raised at such a meeting was to amend the study protocols to continue to follow patients and take samples of their tumors if the patient switched to a different type of chemotherapy, rather than putting them “off study”. Some objected, arguing that there were no clear plans for what to do with those tissue samples; others agreed, arguing that they were “in the discovery phase” and that they should thus “follow the biology.” When one member pointed out that the experiments that could be done using the proposed

additional samples were not in the original study proposals, somebody else sarcastically retorted, “Well, I bet the theory of relativity wasn’t in the proposal either!” (Fieldnotes, March 2012).

The bioclinical nature of new study designs heightens these tensions, because even when researchers agree to operate in “discovery mode” they may disagree about whether to privilege biological or clinical questions. In attempting to solve a problem with slow enrollment in some of the Q-CROC trials, for example, two study PIs (who both managed their trials principally as clinical experimental systems) addressed this same problem differently in order to maximize their chances of producing information about different bioclinical objects: One study PI opted to extend his trial to patients receiving any chemotherapy, reasoning that the biological mechanisms of resistance to chemotherapy were likely similar no matter what type of drug was used. Another PI chose to restrict his inclusion criteria to a single type of chemotherapy and to redouble recruitment efforts, because he believed the specificity of the treatment would allow the team to generate information addressing the clinical question of how to choose one type of chemotherapy over another.

Trialists themselves are aware of such tensions and have put forward multiple suggestions for reforms and organizational innovations that would allow biology-intensive trials to operate more effectively. Cardoso and colleagues (2007) for example, argue that this new generation of trials presents challenges that require interventions at multiple levels, such as new models of collaboration with the pharmaceutical industry

and patient organizations, new considerations of ethical issues and property rights in the collection and use of biological material, and reinforced dialogues between biomedical specialties (p. 249). Abernethy and colleagues (2014) similarly argue that the multiplication of drugs, biomarkers, and hypotheses combined with the present realities of cost constraints has rendered a step-by-step testing-machine approach unmanageable. They suggest that a reframed understanding of the relationship between experimental research and routine care is needed; where experimental protocols can be quickly moved to routine settings, and where data collection infrastructures can turn routine care into a source of clinical evidence that can be fed back into experimental research. Only then will oncologists (and regulators) have a chance to tame the “flourishing pipeline of molecular diagnostic tests, new diagnostic/treatment combinations, and drug-drug combinations” (Abernathy et al., 2014, p. 1064) generated by the bioclinical experimental turn.

Our argument provides an alternative way of thinking about these issues, in that it points to deeper conflicts concerning the assumptions and aims that structure clinical research. We suggest that issues around the execution of biomarker-driven clinical trials that trialists often reduce to organizational concerns (see for example Dilts et al., 2012) may be epiphenomena of a more fundamental conflict between closed and open-ended ways of conceptualizing and operating clinical trials systems. Solutions aimed at problems that are framed as organizational in nature, such as cumbersome bureaucratic requirements or a lack of interdisciplinary communication, may therefore fail to address the more

fundamental issue of how to conduct clinical trials in a manner that allows for more experimental aims and approaches.

Our characterization of the conflicting modes of conceptualizing clinical work also points to an epistemic shift in the field that has implications for the social studies of clinical trials. We propose that the so-called ancillary studies taking place in many clinical trials should not be treated as secondary to the aim of drug evaluation, but should instead be viewed as indications of the emergence of an important new site and style of biomedical knowledge production. Indeed, for some of the trials that we have described here, such as the MINDACT trial, it could be more informative to think of the creation of biobanks of high-quality tissue samples as the central activity, and the stated goal of evaluating whether a new diagnostic test functions better than existing ones as secondary. This frame shift is especially important for analyzing the structure and social implications of trials that come closest to the clinical experimental form we have described here, because treating these trials as though they are solely testing machines ignores a substantial part of their value for researchers, drug companies, and patients.

While this paper has focused on the epistemic issues underlying the organizational problems that confront clinical trial practitioners, the movement towards more experimental styles of clinical research also raises questions about how these shifts are affecting clinical trial participants. In oncology, new forms of clinical trials are changing the calculus of risks and benefits for patients. The same neoadjuvant studies that are highly valued by some clinician-researchers for their ability to generate biological data

from an individual patient also offer new types of information to patients themselves, which they perceive as a valuable way of gaining a better understanding of their own disease (Perlmutter et al., 2012). This points to a final implication of our argument for social science analyses of contemporary oncology and other specialty domains similarly involved in “precision medicine.” The distinction between routine and research has structured a dichotomous understanding of biomedical practices by both social scientists and bioethicists. While in the domain of medical oncology—where today’s experimental protocols are tomorrow’s routine protocols—such a distinction has always been questionable, in recent years it has become even more difficult to maintain. Indeed, following the advent of targeted therapies and translational research, leading oncologists are now pleading for the establishment of more intimate connections between clinical research and routine treatments, as we have noted previously (e.g., Abernethy et al., 2014). The presumption of a sharp distinction between clinical research and clinical care, therefore, is now more than ever a shaky foundation on which to base ethical decision-making for oncology patients (Largent et al., 2011), and new frameworks are needed for thinking about the risks and benefits of scenarios where research and care are inextricably intertwined.

Conclusion

During the past 50 years, US cooperative oncology groups have depicted their activities as clinical experiments, and their organizations as “laboratories without walls” in response to recurrent accusations that their work amounted to mere empiricism (National

Cancer Institute, 2002, p. 29). While historically these claims sometimes functioned more by analogy than substance, in this paper we have identified a transition to a more literal understanding of clinical trials as experimental systems geared towards generating novel and unanticipated biological and clinical insights, and we have emphasized how institutional modalities and experimental sites are changing in order to make such a transition real.

These developments are very much associated with the advent of targeted therapies and biomarker-driven trials that incorporate genomic techniques in oncology, which is somewhat distinct from clinical research in other disease areas (Jones et al., 2011).

Although in recent years there has been a clear trend towards new public-private forms of sponsorship (as with the new National Clinical Trial Network put in place by the NCI; Ong, 2014), cancer clinical trials are conducted primarily in academic medical centers rather than private sector sites, and the trials we have examined here are largely investigator-initiated trials that are funded with public money or charitable donations instead of or in addition to pharmaceutical company sponsorship. These features arguably make the experimental characteristics of clinical trials much more apparent than they might be in trials run by contract research organizations or in other clinical fields, but the trend towards more experimental styles of work in clinical research is not limited to oncology alone. Francis Collins's programmatic vision for improving translational research and drug development at the NIH, for example, evidences many of the same trends we have identified here, such as the desire to foster new public-private partnerships and to move away from the "longstanding but not always reliable practice"

of using animal models for pre-clinical studies and towards systems that use human tissues (Collins, 2011, p. 3). Similarly, the emergence of networked institutions for conducting oncology clinical research is reminiscent of Callon and Rabearisoa's (2008) observation that innovation increasingly originates from competition between networks, the flexible coordination they afford, and the "overflows" (or as we put it, surpluses of knowledge) they generate.

Cancer is one of the main pathologies presently affecting humankind and thus also one of the major pharmaceutical markets. The number of patients and the geographical areas involved in or affected by clinical cancer trials has markedly increased in recent years, and these developments have spurred debates about the social, political, and ethical aspects of clinical research practices. As a precondition for a meaningful discussion one needs minimally to develop a clear understanding of the situation, and we feel that this is decidedly not the case when clinical trials are reduced to mere testing machines. We thus offer this article as an empirically based, conceptually informed clarification of the evolving nature and practices of this form of clinical research.

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Testing Machine	Clinical Experimental System
Set up a protocol to generate a yes or no answer	Ask an (often undefined) question
Deviations are errors (bugs in the system)	Deviations create opportunities for insights (features of the system)
Minimal protocol changes (creating homogeneity)	Protocols in flux (productively managing heterogeneity)
Stable co-operative groups	Ad-hoc consortia
Trial participants as “guinea pigs” for new drugs	Trial participants as a model system for studying bioclinical questions
Closed system	Open ended, evolving system

Table 1: Comparison of the machine and clinical experimental systems views.