AN ADAPTATION FOR CANCER CLINICAL TRIALS: MEDIATING BIASED AND LIMITED ACCRUAL

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By

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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MICROFLUIDICS AND ADAPTIVE CANCER DRUG DEVELOPMENT

Cancer is one of the leading causes of death globally. According to a study of cancer statistics of the United States by Siegel et al (2023), 609 thousand people are projected to die from cancer in 2023, along with 1.9 million new cancer cases projected to occur. While improvements in cancer treatment, early detection, and lifestyle changes have led to a decrease in mortality, improved therapeutics and treatment modalities are clearly needed. One major problem in cancer drug development is the poor success rate, around 3.4%, for novel therapeutics (Wong et al., 2019, p. 273). Common problems with anticancer therapeutics that fail clinical trials include lack of efficacy and off-target toxicity (Lin et al., 2019). These drugs are often developed using in vitro studies that are not reproducible, do not accurately model the tumor microenvironment, and take an average of approximately eight years to bring to patients (Begley & Ellis, 2012; Prinz et al., 2011). Furthermore, these drugs are often biased, with low percentages of racial and ethnic minorities participating in clinical trials, resulting in costly drugs that may be ineffective or even harmful to certain patients (Buffenstein et al., 2023). In order to improve the development, discovery, and effectiveness of cancer drugs, improvements must be made to ensure successful transition towards safe and representative clinical use.

The technical aspect of this project seeks to improve in vitro research of anticancer therapeutics by developing a dual gas and liquid gradient microfluidics system. By designing such a device, the cellular conditions that cancer cells experience can be more accurately modeled and therefore improve the in vitro characterization of cancer cell behavior and expedite cancer drug development. However, developing in vitro tools for improving drug development is not enough to ensure successful clinical transformation nor is it sufficient to guarantee safety and efficacy within different racial and ethnic groups. Thus the tightly coupled STS aspect of this

project seeks to investigate the potential of adaptive design clinical trials in addressing the low representation of racial and ethnic minorities in oncological clinical trials and investigate the risks and benefits such modifications can have on the clinical transformations of developing cancer drugs. Through use of Law & Callon's Actor Network Theory (1988), recommendations for integrating ACTs to resolve the lacking representation in clinical trials can be determined and executed. By improving the in vitro tools for preclinical research and trial methodologies for clinical trials, innovations in cancer clinical research may be further developed and usable to resolve the ever present threat of cancer.

OVERCOMING DEMOGRAPHIC BIAS THROUGH ADAPTIVE CLINICAL CANCER TRIALS

THE BARRIERS TO CANCER CLINICAL TRIALS

In order for a drug to enter the market in the United States, it must undergo clinical trials before receiving FDA approval. The general process of a clinical trial or clinical research begins with an Investigational New Drug application, where the FDA reviews the preclinical research and clinical trial protocol for the drug (Umscheid et al., 2011). The approved clinical trial protocol can include information regarding volunteer selection criteria, duration of trial, data analysis techniques, dosage and type of drug delivery, and other developed details and is then strictly followed throughout the duration of the clinical trial phase (FDA, 2019). Clinical trials often undergo 3 phases with each phase testing different characteristics of the drug on an increasing number of participants. Phase 1 trials observe the safety and dosage schemes of the drug on 20 to 100 volunteers and about 70% drugs pass this phase. Phase 2 trials test the effective dosage and side effects of the drug on several hundreds of volunteers and about 33% of

drugs pass this phase. Phase 3 trials further characterize the efficacy and side effects of the drug on several hundred to several thousand volunteers and about 25-30% of drugs pass this phase. Following the completion of phase 3 trials, the drug can then apply for Investigational New Drug Application where the FDA reviews the information necessary for the drug to enter the market.

Given the number of participants generally required for the completion of each trial phase, clinical trials are dependent on recruitment campaigns, contract research organizations, and medical centers to find patients with a specific condition or disease. Trials that cannot find a sufficient number of volunteers may face increased costs, delays, and potentially early termination. According to a study on reported clinical trials in the Clinicaltrials.gov database by Williams et al. (2015), the leading cause of early termination in clinical trials (68.4% of early terminations) is an insufficient accrual rate or low enrollment of volunteers. Within cancer clinical trials specifically, accrual issues were a major reason for 34.5% of early termination (Zhang & DuBois, 2022). This is not to say that there is a limited population of eligible cancer patients available for cancer clinical trials, rather that there are barriers that are preventing sufficient recruitment. Unger et al. (2016) reports that fewer than 5% of eligible adults participate in cancer clinical trials despite 70% of Americans were found to be likely interested in participating in clinical trials. Major barriers to cancer clinical trials can include access to cancer clinics, health care, clinical trial availability, physician communication, and patient attitude. These barriers unequally impact different demographic and socioeconomic groups and, compounded with the issue of accrual within clinical trials, presents a risk of unintentional clinical trial exclusion of racial and ethnic groups. The results of these barriers to cancer clinical trials is that these clinical trials are poorly representative of the different socio demographic

groups in the trial location as they often rely on an undiversified and unrepresentative patient population.

Clinical trials for cancer drugs suffer from low representation of racial and ethnic groups. According to Loree et al. (2019), comparisons between the distribution in race between 230 reported clinical trials vs the US population revealed that Black (3.1%) and Hispanic (6.1%) patients are usually underrepresented while Asian (18.3%) patients are overrepresented and White (76.3%) patients had around the same proportion in clinical trials as in the US population. Though much of this data is reliant on reported clinical trials that come from PubMed and ClinicalTrials.gov, where reporting race is generally unstandardized and infrequent, it demonstrates the potential differences in volunteer demographics that trial coordinators may face. Further evidence of these demographic disparities can be found in differences in patient recruitment by health care professions, where Niranjan et al. (2020) found that recruitment of minority participants were found to be challenging as potential participants may be perceived with negative prejudices. In some cases, healthcare professionals would screen a patient's socioeconomic background and withhold information to patients that were viewed to be non-ideal. Additionally, perceptions of clinical trials can differ between racial groups, with particularly the Tuskegee syphilis study as a critical example of how historical influences continue to affect perceptions and distrust towards clinical trials (Diehl et al., 2011). Participants may also be dissuaded from participating due to distance and economic barriers, further highlighting the importance of recruiting local healthcare centers and further improving local health infrastructure. These different barriers are critical to understanding the cause of the demographic biases in clinical trials and need to be addressed within cancer clinical trials to ensure that cancer treatments are safe for any and all individuals suffering from cancer.

Given these considerations associated with demographic biases in cancer clinical trials, developing measures to minimize the potential risks that demographic biases present need to be further embraced. It therefore requires identifying and understanding the risks, training, and necessary steps to introduce diversification into the process of cancer clinical trials. As such the use of Carlson (2009) theoretical science, technology, and society (STS) framework, the Handoff model should be employed. Between each handoff, the risks and requirements of each party encounter are detailed to showcase how an idea or technology comes to fruition in society. In the case of cancer drug development, the Handoff model is an appropriate model given the regulatory pathway for clinical transformation shown in Figure 1.

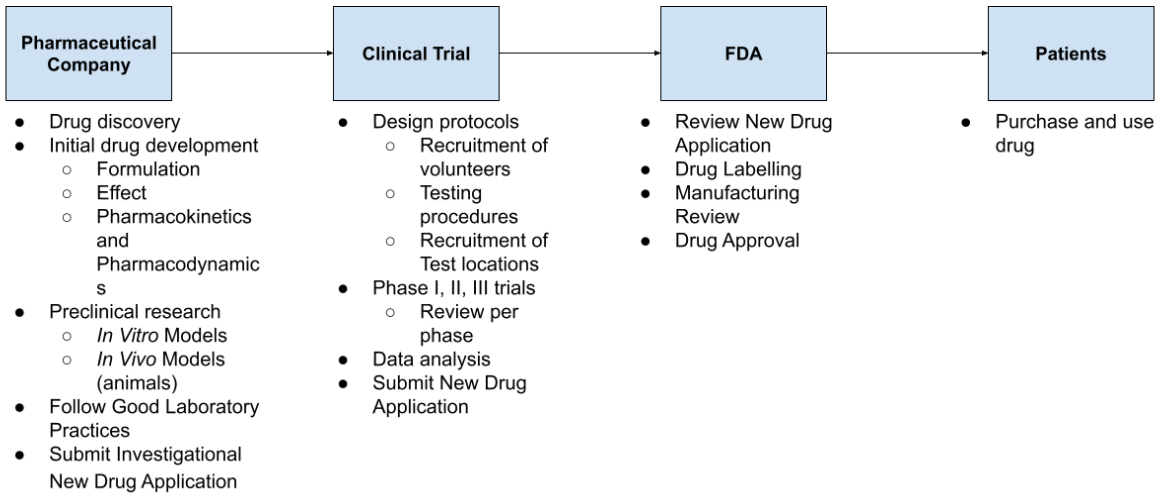

Figure 1. Handoff model of Drug Development. Each party must complete the list of actions below to ensure safe and effective drug development (Carlson 2009).

Pharmaceutical companies invest time and money to discover and characterize the effects of the drug through preclinical research. The drug enters pending approval and then undergoes clinical trials where participants are needed to evaluate the drug's efficacy and safety. The FDA then examines the data obtained by the trial and decides whether the drug has been sufficiently

characterized and safe for clinical use. Completion of each task by each party along the Handoff model is critical to ensure that patients can purchase the safe and effective drug to treat their disease.

RISKS OF INACCURATE REPRESENTATION

There are numerous risks associated with incompletions within the drug development Handoff model. As seen in Figure 1, the different applications needed to be submitted serve as blockades between each party to ensure successful completion required tasks. For example, if the cancer drug was found to be ineffective in preclinical research, then an Investigation New Drug Application would not be approved. In most cases, if a harmful or ineffective drug happens to bypass the earlier blockades it generally will fail within the clinical trials phases. In cases where a clinical trial is found to be biased, additional safeguards need to be implemented to ensure that biases are detected and prevented. Thus methods for improving health equality and relaxing barriers for diverse enrollment of clinical trial volunteers should be considered between each clinical trial phase to ensure successful and representative participation of racial and ethnic groups is followed. Methods may include improving patient and healthcare professional relationships and trust, employing multiple local health centers for recruitment and trial participation, and even considerations regarding participation compensation.

Though understanding preventative measures against demographic bias in cancer clinical trials is critical, understanding the potential consequences of these biases can have on clinical trials is also especially important. According to Hamel et al. (2016), low enrollment of racial and ethnic minorities may impact the treatment outcomes and survival of minority patients. The major mechanisms that lead to cancer lie within the interactions between environmental factors

and an individual's genome, as such the response an individual may have towards treatments that target specific genomic and cell signaling receptors can vary. According to Ma et al. (2010), the distribution of genetic mutations in lung, breast, colorectal, and gastric cancers can vary across ethnic groups as different groups may have a higher or lower expression of certain enzymes, receptors, and cell types that are associated with higher risks towards or better protections against cancer. For example, Ma et al. noted that Chinese, Korean, and Japanese female non-smokers have been found to have a higher prevalence for lung cancer due to a higher probability of developing mutations in their epidermal growth factor receptor protein. An individual's genes may also impact their response to cancer and anticancer drugs. According to Oh et al. (2015), an individual's genes may also impact the symptoms that one experiences while affected by cancer, their metabolism of certain drugs, and even impact the severity and mortality rates of certain cancer types. The combination of these different variabilities and their potential effects in cancer therapeutics may have costly effects on racial and ethnic groups seeking cancer treatment, especially if employing biased and slightly less effective therapeutics. As such, there is a need to diversify patient populations to better evaluate generalizability of anticancer therapeutics in clinical trials.

The costs of an undiversified clinical trial cohort also impacts the economic burden of cancer and speed in innovation for cancer drugs. It is estimated that health inequalities between 2003-2006 costed the U.S. $1.24 trillion dollars when adjusted for inflation to 2008 (LaVeist et al., 2011). While it is unknown how much the cost of health inequalities were the result of cancer specifically, clinical research for cancer has displayed similar trends and concerns regarding demographic disparities. Another aspect regarding the cost of this demographic disparity is within the advancement of new treatments and increased survival rates. When comparing cancer

clinical trial enrollment rates for adults against the historically higher enrollment rates for children, Unger et al. (2016), notes that these higher enrollment rates are consistent with decreasing rates of cancer mortality within children less than 15 years old. It is clear the additional cost of demographic biases in cancer clinical trials leads to increased economic burden and decreases to treatment innovations for cancer, further compounding the mortality of cancer.

THE WEAKNESS OF RANDOMIZED CONTROL CLINICAL TRIALS

Though resolving demographic biases may occur through evaluating and implementing new measures between each clinical trial phase to decrease the risk of lack of diversity, this method will likely require long-term investment that will likely not come to fruition within the same timeframe of future innovations, such as better *in vitro* models, in discovery and developments in cancer interventions. The current problem facing cancer clinical trials is a compounding lack of minority enrollment into trials and the lack of generalizability of results from racially or ethnically biased clinical trials. As such continued reliance on "gold standard" methods for clinical trials, the randomized controlled trials (RCTs), may not be reasonable for cancer clinical trials until long-term changes to volunteer accrual can be implemented.

RCTs are double blinded trials schemes notable for their ability to eliminate bias and capabilities in examining the causal relationships between drug and health outcome (McDonald et al., 2006; Nair, 2019). Trial participants are randomized and assigned to placebo or different drug dosage groups without the knowledge of the participants nor the researchers themselves. The problem with RCTs in cancer clinical trials is that RCTs require a large number of volunteers in order to determine the effects of drugs with sufficient statistical power. Given the lack of

minority participation in clinical trials, reliance on RCT to resolve racial or ethnic biases is not feasible.

ADAPTIVE DESIGN TO MEDIATE DEMOGRAPHIC BIASES

Recently, a new regulatory pathway has been accepted within the FDA to accelerate clinical trials (Wang, 2013). Known as adaptive design or adaptive clinical trials (ACTs), these clinical trials allow for preplanned modifications to trial procedures and use of statistical analysis to generate information on drug safety and efficacy (Bhatt & Mehta, 2016). In particular, ACTs can allow for sample size refinements, focused recruitment efforts, changing ratios of patients in different dosage groups, and introducing checkpoints for early terminations (Pallmann et al., 2018). While some of these modifications may be able to overcome the lack of diversity, through modifications such as sample size readjustment and pick-the-winner/drop-the-loser, implementation of preplanned stops can also be used to ensure patients are protected against potential harmful trial schemes and build further trust in clinical trials. In order to ensure that ACTs can overcome the lack of diversity, procedures and regulations should be in place to protect volunteers and ensure that clinical trials are carried out ethically and safely.

As such, given the numerous and complex relationships that exist between the different actors involved with the drug development process, the use of Actor Network Theory (ANT) should be employed to examine potential gaps and measures that should be implemented to ensure effective use of ACTs (Law & Callon, 1988). ANT maps the material, societal, and symbolic elements of a network to examine the relationships between them as seen in Figure 2. The main actors involved in this map of a typical clinical trial are the pharmaceutical companies

who develop and market drugs, the FDA who reviews clinical trials and monitors drug safety, and the patient who provides patient data and receives the drug for treatment.

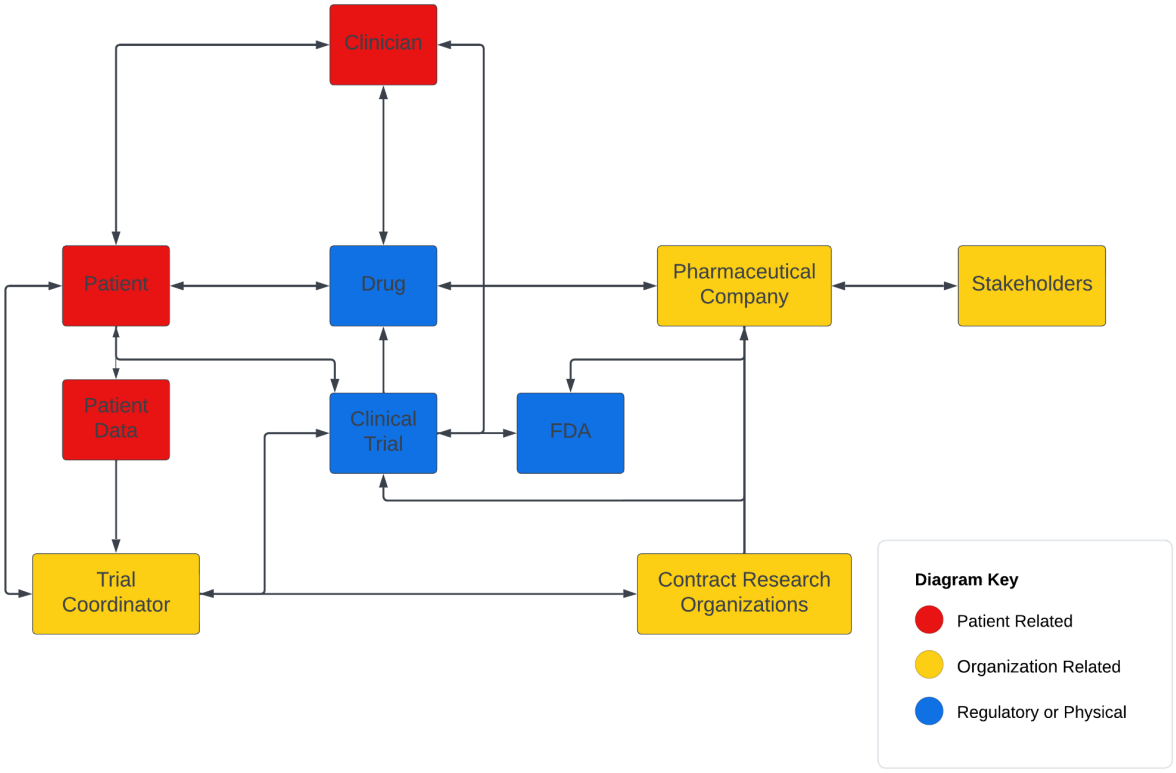

Figure 2. Actor Network Theory Map of Typical Drug Development. (Jian, 2022)

Under such typical conditions of cancer drug development, should patient data be found to be biased or unrepresentative of the trial site then it immediately falls onto the Trial Coordinator to discover and resolve this issue. One problem with this is that clinical trial procedures, once set, are to be strictly followed meaning that actions that a clinical trial coordinator can perform to rescue a clinical trial are limited. In addition, should the trial coordinator be unable to discern or address this lack of representation, then the drug that develops from the completion of said clinical trial may be ineffective for certain patients resulting in downstream problems for the

different actors within the ANT map. Regardless of which scenario occurs, the resulting drug may end up failing clinical trials or found to be questionable in efficacy and avoided when clinicians prescribe a patient with cancer drugs.

For mapping ACTs with ANT, a number of changes can be seen when compared with the typical drug development ANT as seen in Figure 3. Though most of the relationships between the different actors and actants remain the same, the relationships between the Patients, the Trial Coordinators, and the Clinical Trial itself are expanded.

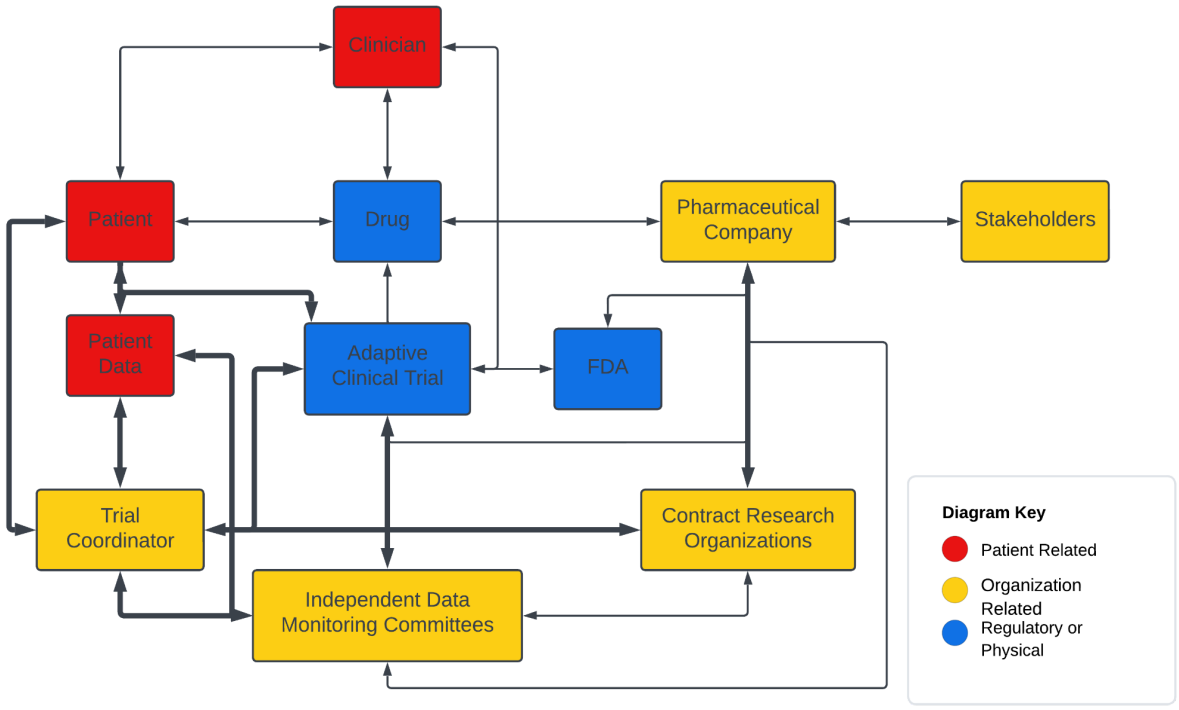

Figure 3. Actor Network Theory Map of Adaptive Design Drug Development. The additional bold arrow lines demonstrate expanded relationships between different actors. (Jian, 2022)

Due to the nature of ACTs requiring statistical analysis of trial data whilst the trial is running, an additional actor that performs the necessary statistical analysis is needed for successful adaptive trial execution. Though this actor may be a part of the trial coordinator team, the decisions and

analysis they perform is nevertheless independent from the responsibilities of the trial coordinator in managing the ACT. The result of the expanded relationships between the different actors, when compared to the typical drug development process, allows for the characteristic flexibility of ACTs in executing the preplanned procedural changes. If the volunteer patient population is found to be biased by the Independent Data Monitoring Committee, then trial modifications can begin with the Trial Coordinator and affect its related actors and actants such that racial biases can be overcomed.

Through ANT analysis and further research, potential ethical and regulatory concerns can be determined between the different elements of the ANT network. By determining these concerns, it will be possible to recommend regulatory and procedure changes for affected elements within the network and equitably develop and provide safe and effective anticancer therapeutics. In the case of widespread implementation of ACTs, critical relationships need to be established between the clinical trial coordinators, regulators, and data monitoring committees. In ACTs, data analysis occurs during ongoing trials and as such relationships must be established between trial coordinators, regulators and data monitoring committees. The purpose of such relationships ensures that data analysis can be performed rapidly and accurately as trial coordinators may not be familiar with ACT statistical analysis techniques. Establishing further relationships with regulatory agencies ensures early notification of terminations and trial phase changes and reporting of patient demographic data. Should data monitoring committees discover racial or ethnic biases present within the volunteer population, ACT adjustments such as sample size readjustment or coordination with trial coordinators for additional recruitment campaigns may be employed. The end result of implementing ACTs within cancer clinical trials would

ensure rapid and responsive measures during ongoing clinical trials to protect volunteers and respond to demographic biases.

IMPROVING CANCER DRUG DEVELOPMENT

Resolving demographic biases is an ongoing issue within drug development. In the case of cancer drug development where eligible volunteer populations are especially limited due to the various types of cancer, improvements to recruitment campaigns for greater demographic diversity may be incapable of resolving racial or ethnic biases. Furthermore, ACTs are advantageous to "gold standards' like RCTs as flexibility in trial design allows for far more diverse weigh in and negotiation between different actors within drug development and responsive measures in trial adaptations and reflective trial progression. As such implementation of ACTs should be further explored within cancer drug development as a safer and more equitable clinical trial methodology.

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