Journal of Health Science & Education
An open access journal
eSciRes
JHSE-1-158
Research Article

Ready, Willing, and Able to Participate in Cancer Clinical Trials: Insights from a Theory on Fertility Transition

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Abstract

Background: Controlled clinical trials are considered the gold standard for cancer treatment and vital in the development of leading cancer therapies. One of the major challenges in cancer clinical trials (CCTs) is the lack of patient participation. **Aim:** Borrowing insights from Ansley Coale's theory on fertility transition that identifies three preconditions (ready, willing, able) for fertility decline, this study seeks to illustrate how this Ready-Willing-Able (RWA) framework can explain participation in cancer clinical trials (CCT) for both patients and healthcare providers based on related literature. **Materials and Methods:** Based on the RWA framework, search terms were developed to provide a comprehensive examination of barriers and enablers associated with CCT participation from both patient and care provider perspectives. A systematic search of literature was conducted at electronic databases including PubMed, Scopus, and EMBASE to identify 114 relevant studies published between January 2008 and May 2017 for data abstraction. **Results:** A host of factors at individual, organizational, regional, and health care system levels can respectively impact the readiness, willingness, and capacity for CCT participation amongst patients and healthcare providers. Meanwhile, the readiness, willingness, and capacity for CCT participation on either side can further influence and be influenced by patient-provider communications before the patient makes his or her decision over CCT participation. The three aspects of CCT participation on the patient and provider sides are constrained by contextual factors at the organizational, regional, and healthcare system levels that can determine not only the availability and distribution of CCTs but also whether and the extent to which the infrastructure and organizational support for CCT implementation are in place. **Discussion and Conclusion:** The RWA framework was instrumental for identifying and streamlining various, multilevel factors impacting CCT participation by both patients and healthcare providers. The weakest link principle of the RWA framework suggested that there might be unique barriers for different groups of patients or healthcare providers that have prohibited them from being ready, willing, or able to participate in CCTs.

Keywords: Cancer clinical trial participation; Ready; Willing; Able; Contextual factors

Introduction

Controlled clinical trials are considered the gold standard for cancer treatment and vital in the development of leading cancer therapies. One of the major challenges in cancer clinical trials (CCTs) is the lack of patient participation. In 2010, it was estimated that only 3% of adult cancer patients participated in CCTs and 40% of trials failed to accrue the minimum number of patients required for adequate trial participation [1]. A review of therapeutic trials supported by the National Cancer Institute between 2000 and 2007 suggested that over 80% of these trials did not achieve projected accrual goals within the anticipated periods [2].

Various factors can impact the chance for cancer patients to be enrolled into clinical trials. Patient accrual to clinical trials usually involves several stages including trial availability, study eligibility, physician triage, presentation of trials, determination of patient interest and barriers, and acquisition of informed consent and enrollment [3]. There are documented barriers associated with each of these stages such as the lack of awareness of trials [4,5], restrictive eligibility criteria (e.g., age and comorbidity) [6,7], mistrust of research and the medical system by patients [8,9], patient concerns about efficacy and safety of trials, financial costs, randomization, trial burden, loss of confidentiality, and cultural or linguistic barriers [10,11]. Residential distance from an academic or cancer center can also hamper the feasibility of trail participation for some cancer patients [12]. Administrative barriers including structural, infrastructural, and procedural obstacles to patient accrual have also been found to deter the implementation of CCTs [13].

In light of the multifaceted barriers related to the accrual of CCTs, several studies developed conceptual frameworks seeking to address, integrate, and streamline these factors [14-16]. Based on a systematic review of the related literature, one of the most cited conceptual models focused on three key barriers to recruiting underrepresented cancer patients to CCTs including awareness, opportunity, and acceptance [15]. The basic premise of the Ford Model is that in order for a patient to participate in a trial, the patient must be aware that the study is being conducted and that he or she can have the opportunity to participate. Under this conceptual model, identified barriers to trial awareness included lack of education, lack of culturally appropriate information, limited cancer knowledge, and lack of physician awareness of trials. Major barriers for opportunity to participate were old age, low socioeconomic status (SES), racial and ethnic minority status, study eligibility and exclusion criteria, provider attitudes, lack of provider referral, and lack of patient-provider communication regarding trials. Common barriers to acceptance of trial enrollment based on the Ford Model included mistrust of the research and medical system, perceived harms of clinical trial participation, loss of control (uncertainty about treatment allocation), time commitment, loss of income, and transportation.

Despite its insights into CCT participation, the Ford Model has several limitations. One limitation concerns the model's exclusive focus on underrepresented populations in terms of their barriers to CCT participation. Consequently, the model's relevance in explaining CCT participation among the general population remains unclear. While the Ford Model identifies awareness, opportunity, and patient acceptance as three key determinants of CCT participation, the model does not explicitly specify and differentiate how these three determinants are respectively linked to factors associated with patients, providers, and patient-provider communication. Furthermore, the conceptual framework adopted by the Ford Model fails to consider how contextual factors at the organizational, regional, and health care system levels constrained the options of patients and their care providers regarding CCT participation.

Aims of the Study

In an effort to expand and improve the Ford Model, the purpose of this study is to develop a new conceptual framework based on factors related to participation in CCTs among the general cancer patient population. In particular, this study utilizes insights from an influential theory on fertility decline in demography [17] to examine the prohibiting and enabling factors of patient accrual to CCTs based on a systematic review of recent literature on CCT participation in the United States. Given the importance of physician triage and referrals in patient accrual to CCTs, our newly developed framework differentiates factors related to patients from those of the physicians or trial providers in general. The framework also encompasses contextual factors at the organizational, regional, and healthcare system levels that would impact the chance for patients and their care providers to participate in CCTs and confine their options, which, to our best knowledge, has not been systematically examined in previous studies.

Conceptual framework

One of the most fundamental changes to the global population in the modern era has been the so-called 'demographic transition' which denotes the transformation of the global population from high mortality, high fertility regime to a regime characterized by low mortality and fertility [18]. One influential theory suggested three preconditions for fertility decline: (i) fertility must be within the calculus of conscious choice for individuals or couples; (ii) reduced fertility must be perceived to be socially and economically advantageous; and (iii) effective techniques of fertility reduction must be available and not excessively costly [17,19]. These three preconditions have been respectively abbreviated as 'ready', 'willing', and 'able' (RWA) in some of the subsequent citations of Coale's theory [20,21]. According to Coale, 'ready' correspondingly means that people realize fertility is an important aspect of life that they can have personal control of; that is, fertility decisions, such as whether and when to have children, as well as how many children to have, are not something totally prescribed or dictated by religious or cultural values [22]. The RWA framework hinges on the weakest link principle, that is, it is the minimum of either 'R', 'W', or 'A' that determines the final speed of the adoption of fertility regulation (either for spacing or stopping) and different factors may be responsible for the pace of fertility transition in different populations [20].

Based on a review of relevant literature, we argue that the RWA framework can offer unique insights into CCT participation by cancer patients. In particular, 'ready' in this case means that cancer patients are aware of CCTs and can make informed decisions over whether to participate in CCTs based on their knowledge of CCTs; 'willing' means that patients need to be convinced that participation in CCTs is beneficial for their cancer treatment and/or the advancement in cancer treatment; and 'able' refers to the ability for patients to participate in CCTs, that is, patients should have the necessary resources and support (e.g., insurance coverage, family support, transportation, time commitment, and so forth) that would allow them to participate in CCTs.

The RWA framework can also be applied to healthcare providers who play a critical role in patients' participation in CCTs [23]. Physician referrals constitute the most important source of CCT awareness for patients [5,24]. 'Ready' on the provider side means that a provider is either in charge of, participates as an investigator in a CCT, or is at least knowledgeable or aware of a CCT, which would allow the provider to introduce the trial to a patient. 'Willing' means that, based on his or her assessment of a patient's disease condition, eligibility, and the therapy provided through the trial, the provider sees the benefit for patient participation and is willing to refer the patient to the trial. Lastly, 'Able' on the provider side means that the provider has the needed organizational and administrative support to successfully engage, recruit, refer, retain, monitor, and serve patients in a CCT.

For patients and healthcare providers, the chance of CCT participation is also contingent upon a series of contextual factors at the regional, healthcare system, organizational, and community levels. These factors include, but are not limited to, availability of CCTs in the region, distance from patient homes to the trial sites, transportation, health insurance coverage for patient participation, organizational support for CCTs, and community engagement and partnerships. Since CCTs are usually concentrated in academic health science centers, physicians and patients might have differential exposure to and awareness of CCTs depending on their geographic locations. Patients from rural or medically underserved areas usually face unique access barriers due to unavailability of active CCTs [25].

Based on the RWA framework (Figure 1), contextual factors at the regional, healthcare system, organizational, and community levels confine the options providers and patients have for CCT participation. Patient-level factors can impact patients' readiness, willingness, and ability to participate in CCTs, whereas provider-level factors can impact providers' readiness, willingness, and ability for CCT participation. Factors at the patient and provider levels can jointly influence patient-provider communication, which in turn will influence patients' decision on CCT participation. At the same time, patient-provider communication will also influence the readiness, willingness, and ability of CCT participation on either the patient or provider side.

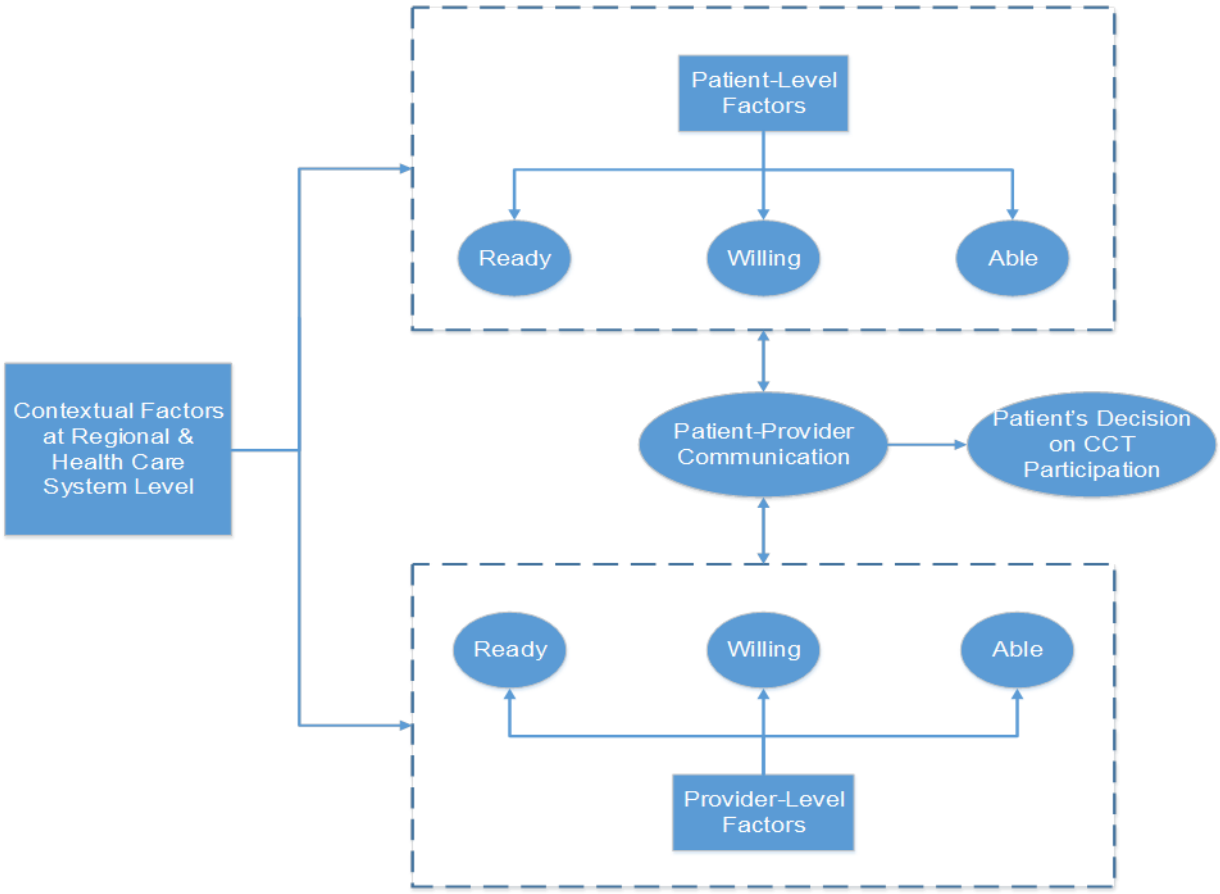

Figure 1: The ready-willing-able framework on cancer clinical trial participation.

Materials and Methods (Literature Search)

The literature search for this study sought to identify published studies pertaining to the various barriers affecting patient participation in cancer clinical trials. Considering the large number of studies in this area, we restricted our search to relevant publications between January 2008 and May 2017 in order to focus on recent findings. Based on the RWA framework, search terms were developed to provide a comprehensive examination of barriers and enablers associated with CCT participation from both patient and care provider perspectives. The following search terms were utilized in the literature search: "awareness of cancer clinical trials"; "barriers for cancer clinical trials"; "disparities in cancer clinical trials"; "minority participation in cancer clinical trials"; "perception of cancer clinical trials"; "physician referral for cancer clinical trials"; "predictors for cancer clinical trials"; "promotion of cancer clinical trials"; "willingness to participate in cancer clinical trials"; "eligibility for participation in cancer clinical trials"; and, "cancer fatalism"." Inclusion criteria were: (1) studies published between January 2008 and May 2017; (2) samples from the U.S.; (3) peer-reviewed full-length research articles. Exclusion criteria included: (1) conference papers and

abstracts; (2) dissertations and theses; (3) studies focused on cancer screening instead of cancer clinical trials; and (4) review papers.

A systematic search of literature was conducted through electronic databases including PubMed, Scopus, and EMBASE to identify relevant studies. To increase objectivity, two reviewers (S.R. and J.Q) first independently conducted the literature search based on the search terms, inclusion and exclusion criteria, and identified electronic databases before they compared their search results and agreed on the final list of the included articles. The process of the literature search is illustrated in Figure 2. Based on our selected key words, 473 records were initially identified from the three electronic databases. After removing duplicates and ineligible articles, 114 publications were included in the literature base.

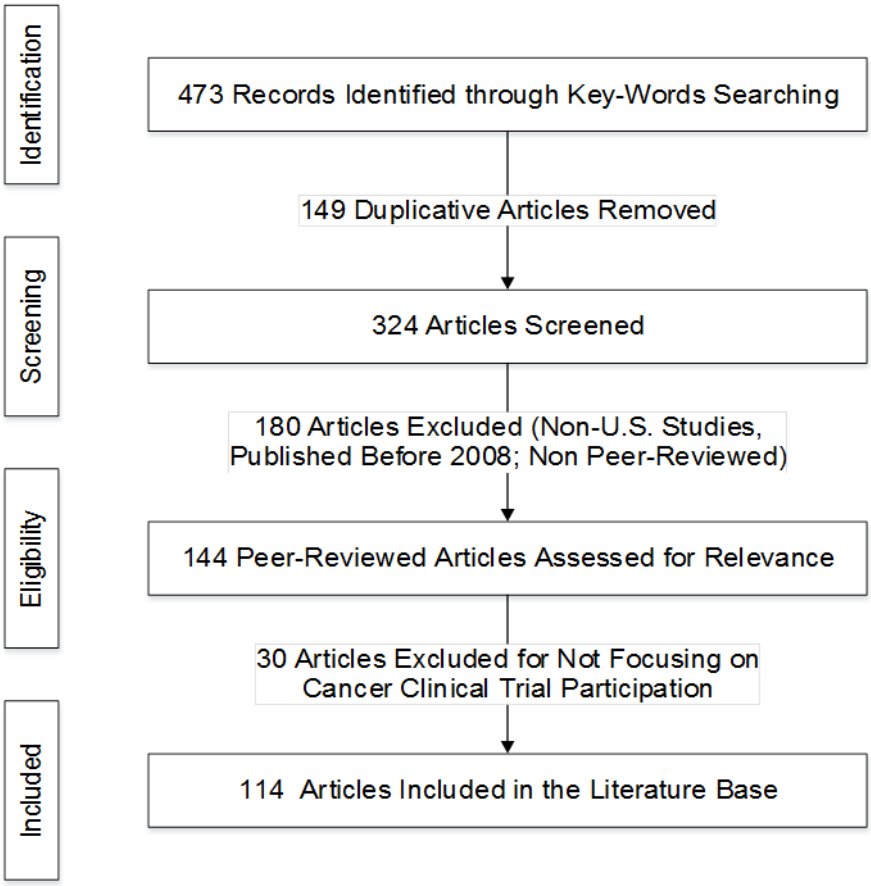

Figure 2: Process of literature search.

Results

We organized the results section based on each of the components (ready, willing, able respectively on the patient and provider sides, patient-provider communication, and contextual factors) as illustrated in our proposed conceptual framework. For each component, we examined the 114 identified articles in the literature base and identified findings relevant to the component.

A. Factors on the Patient Side

1) Patients' readiness to participate in cancer clinical trials

One of the key determinants of patients' readiness for CCT participation concerns is patients' awareness and knowledge of trials. Estimates based on national survey data suggest that overall clinical trial awareness among adult Americans increased from 68% in 2008 to 74% in 2012 [26]. One study found that among first-degree relatives of cancer patients, 45% of them were unaware of cancer prevention clinical trials [27]. There were substantial racial, ethnic, and SES disparities in awareness of trials. Racial and ethnic minorities were found less likely than non-Hispanic Whites to be aware of clinical trials. In addition, higher SES, as indicated by income or education, was associated with an increased awareness of clinical trials [24,26,28-31]. Estimates based on a nationally representative sample of American adults indicated that the percentage of respondents who reported awareness of clinical trials among Whites, African Americans, Asian Americans, and Native Americans were 71.9%, 57.3%, 46.3%, and 37.4% respectively [28]. According to the same study, 46.5% of Hispanic respondents reported awareness compared to 69.7% among non-Hispanic respondents.

Some of the racial and ethnic differences in awareness of CCTs could be related to health literacy. Based on qualitative data collected through focus group discussions with African Americans and Hispanics, one study identified misconceptions related to scientific information and common

perceptions of clinical trials such as uncertainty and fear [32]. In another similar study of Hispanic cancer patients and their caregivers, it was revealed that the participants demonstrated low levels of knowledge about clinical trials, uncertainty about why a physician would expect a patient to make a choice about treatment, as well as a desire for family participation in decision making [33,34]. In another study focusing on Chinese Americans, health literate cancer communication was found to be vital in recruiting patients [35].

One study used the Ottawa Decision Support Framework to evaluate how clinical trial knowledge, attitude-related barriers to trial participation, and patient self-efficacy among 1,256 cancer patients could impact their readiness for trial participation [36]. It was found that patients' knowledge about cancer clinical trials directly impacts their preparedness. Greater knowledge allows patients to make more informed decisions regarding their participation in CCTs. Self-efficacy mediated the associations between attitude-related barriers and preparedness. The study concluded that assessing patients' level of self-efficacy may be just as important as evaluating their knowledge and attitudes about cancer clinical trials.

Physicians are the primary source of information for patients to know about CCTs [5,24,37]. Based on data from a survey of 184 patients with pancreatic cancer and 213 caregivers, only 12% of the patients participated in a clinical trial [5]. For these patients, physicians were listed as the primary source (80.4%) of trial information 80.4% of the time. About half of the respondents (49.1%) indicated that they had never discussed clinical trials with a physician, suggesting the need of increasing physician-patient discussion to promote patient participation in CCTs.

The Internet is another important source for patients to learn about CCTs, especially for patients in U.S. urban areas [38]. There was evidence that having websites with information on cancer, treatment, and clinical trials can improve communication between physicians and patients, and increase patients' knowledge about cancer [39,40]. One study simulated the experience of a naïve cancer patient without clinical trial knowledge by searching three popular search engines for treatment information for breast, lung, and prostate cancer, and myelodysplastic syndromes [41]. The findings suggested that although cancer clinical trial information was widely available on the Internet, overall readability was poor and information quality was highly variable across websites. The study concluded that interactive web-based interfaces could serve as powerful vehicles to help patients locate appropriate clinical trials, although there was room for many of these interfaces to be improved.

Cancer fear and fatalism can negatively impact patient readiness for trial participation. Cancer fatalism, which can be described as "deterministic thoughts about the external causes of the disease, the inability to prevent it, and the inevitability of death at diagnosis" [42], or a pessimistic view that cancer is uncontrollable and lethal [43], is an important barrier to participation in cancer screening and treatment [43,44]. Patients with a higher level of cancer fear and fatalism were less likely to learn about positive developments and advances in cancer control and treatment [45], which can lead to no or low participation in clinical trials.

The majority of U.S. adults endorsed one or more fatalistic beliefs about cancer [46]. A fatalistic attitude towards cancer was more commonly observed in individuals with lower SES, older age, racial and ethnic minority status, and a family history of cancer [43,47-49]. There was also evidence that rural residents were more likely to endorse multiple fatalistic beliefs about cancer prevention than urban residents after controlling for related demographic correlates [38]. Relative to non-Hispanic White patients, low-income minority patients were more likely to have late-stage cancer diagnoses, less likely to undergo treatment, and consequently to have higher mortality rates [50]. Due to delayed diagnoses, some researchers found that minority patients were overrepresented in advanced-staged cancer trials [51].

Eligibility is an important component of patient's' readiness for CCTs. Specific eligibility requirements based on age, gender, race and ethnicity, type of cancer, stage of cancer, and so forth exclude many patients from participation [52,53]. One study examined barriers to enrollment in non-small cell lung cancer therapeutic clinical trials among 183 patients with appropriate disease and stage of the disease [54]. Over 55% of these patients were ineligible for trial participation because of poor performance status (18%), need for emergent radiation (12%), lack of adequate staging information (6%), and comorbid conditions (4.9%). Findings from another study also suggested that patients with more comorbidities were less likely to qualify for trials [29]. However, there was evidence suggesting that eligibility criteria were not significant barriers to enrollment. For example, one study reported that within randomized phase II and III adjuvant and neoadjuvant breast cancer trials, eligibility was not a significant barrier [55].

2) Patients' willingness to participate in cancer clinical trials

Cancer patients are usually more likely to participate in CCTs when they are convinced of the treatment efficacy or how the trial results could advance cancer treatments and benefit other patients. Moorcraft et al. [56] found that the top two reasons patients cited for their participation in CCTs were 1) 'the trial offered the best treatment available' and 2) that 'the trial results could benefit others'. This study concluded that patients' motivations for trial participation included perceived personal benefit and altruistic reasons. Similar findings were also reported from a study by Sprague et al. [57] on factors related to willingness to participate in CCTs among American Indians and Alaska Natives.

There was evidence that willingness to participate in CCTs could be related to stage of cancer diagnosis. Swain-Cabriales et al. [58] found that patients with stage II or III breast cancer were more likely to be enrolled in a trial compared to patients with early-stage breast cancer. This finding, however, contradicts with findings of Housri et al. [59] from another study where they revealed that breast cancer patients with more advanced tumor stages were less likely to enroll in radiation oncology clinical trials. Consistent with this finding, Gerber et al. [25] reported that cancer patients were

most open to participation in clinical research shortly after diagnosis, specifically within 30 days of diagnosis.

Another major factor influencing willingness to participate (WTP) in CCTs is trust in clinical trials or medical professionals who implement these trials, which has not been evenly distributed across racial and ethnic groups. Relative to White cancer patients, African American cancer patients were more likely to express distrust in CCTs [60,61]. Similar findings were also reported from another study where it was reported that African American and Hispanic participants had more negative attitudes about clinical trials, more distrust toward doctors, and less willingness to participate in clinical trials than non-Hispanic Whites [62]. Another related study examined how knowledge, distrust, information sources, and religiosity impact WTP in CCTs among Caucasians and African Americans [63]. Findings from this study suggested that distrust in medical professionals was a strong barrier to WTP for both groups, whereas factual knowledge about trial procedures was not associated with WTP for either group. It was also found that levels of religious activity negatively predicted WTP for Caucasians but positively predicted WTP for African Americans. Among Latinas who prefer Spanish physicians, it was found that intrinsic religiosity was associated with mistrust in clinical trials among Spanish language-preference Latinas [64].

Findings based on an assessment of WTP in a hypothetical CCT among Native Americans revealed both enabling and prohibiting factors associated with WTP [65]. The enabling factors included having a lead researcher of Native descent, having a study physician with experience treating American Indians/Alaska Natives, personal experience with the cancer being studied, family support for participation, and belief/hope that the study would result in new treatments. The prohibiting factors identified by the same study included living far from the study site and a high risk that confidentiality could be breached.

Patients' self-efficacy constitutes another determinant of WTP in clinical trials. Based on survey data from 944 Spanish-speaking, immigrant Latinos using safety net clinics, Wallington et al. [24] one study identified correlates of WTP in CCTs. It was found that higher self-efficacy among immigrant Latinos was associated with intent to participate in CCTs. Similar findings were reported in another study where it was found that self-efficacy can facilitate the decision-making of cancer patients about their participation in CCTs [66].

3) Patients' ability to participate in cancer clinical trials

Besides readiness and willingness for CCT participation, patients should also have the necessary resources and support to successfully complete their participation in cancer clinical trials. One of the most significant barriers concerns health insurance coverage for CCT participation, which is especially important in consideration of startup costs as a major cause for trial non-activation [25]. For example, from 2003 to 2008, Johns Hopkins submitted insurance requests for 4,617 consented cancer patients, out of which 628 patients (13.6%) with health insurance were denied therapeutic trial enrollment due to lack of insurance coverage for participation in CCTs [67]. The study concluded that denial of insurance coverage for CCT participation, even among insured patients, constituted an important barrier. Some patients who do have insurance may still not participate in CCTs due to fear that their insurance coverage may not cover the cost [54,68-70]. Financial counseling can facilitate accrual to CCTs amongst minority populations (Virani et al.), as cost was often cited as a major barrier in CCT participation among financially disadvantaged minority populations [71].

Logistical barriers such as transportation or time demands for CCT participation have also been documented [72]. Based on in-person surveys of 300 elderly patients with advanced tumors who had received prior chemotherapy, 34% reported driving to the trial site and the needed time for trial participation as a major logistical barrier [73]. Long distances to the trial site (>50 miles) was also found to discourage Native American adults from CCT participation [57]. These logistic barriers further affect patients' SES. Since patients with higher SES presumably have more resources to overcome the logistical barriers to CCT participation, this relationship can help explain the documented positive associations between patients' SES and CCT participation [74,75].

Language constitutes an important barrier to CCT participation for patients with limited English proficiency [60]. The proportion of clinical trials that require English fluency for study inclusion increased substantially, from 1.7% before 2000 to 9% after 2010 [76]. Bilingual web materials, print materials, and points of contact may help improve minority patient recruitment in CCTs [77]. Based on qualitative data collected from principal investigators and CCT administrators, one study reported that non-English–speaking patients often were not recruited because of the expense of making consent forms and recruitment materials available in multiple languages [69].

B. Factors on the provider side

1) Providers' readiness for CCT participation

Providers' perceived unavailability of clinical trials was shown to be a major barrier to enrolling breast cancer patients into clinical trials [78]. The rarity of CCTs and lack of awareness of CCTs on the part of providers were also identified as obstacles for the inclusion of teenagers and young adults in the CCTs [79]. Even when CCTs are available, some providers might be unaware of the trials. The reasons behind this lack of awareness can be complex, and it remains unclear whether the unawareness is mainly caused by an actual lack of information about trials or a lack of motivation to take advantage of existing resources to become aware of available trials [80]. One study cited interdisciplinary structure at breast specialty clinics as a factor contributing to providers' lack of awareness of trials because such a structure fails to assign patients to a specific provider [81].

Besides availability and awareness of CCTs, providers' readiness for CCT participation is also contingent upon their knowledge of CCTs. Based on data collected from 111 oncologists in Texas, one study reported that familiarity with clinical trials and their local availability was significantly

related to referring patients to the trials [82]. Recommendations from another study included the establishment of user-friendly, up-to-date, and easily accessible centralized registry of CCTs to ensure information access for physicians [83]. Such an arrangement can also help nurse practitioners when they recommended trials to patients [84]. There was also evidence that providing education on CCTs to primary care providers (PCPs) can increase the chance for PCPs to mention trials to their patients [85].

2) Providers' willingness to refer patients to CCTs

Providers' willingness to refer patients to CCTs is closely related to providers' perceptions, values, and beliefs of CCTs. There was evidence that oncologists were more likely to refer patients to CCTs when they perceived the value of the trials [80,86]. Based on qualitative data collected from 27 PCPs serving predominantly minority populations, one study reported that it was pretty common for the providers to express disinterest in CCTs and to have misconceptions about the quality of care received through CCTs [70]. The study concluded that targeted, evidenced-based educational interventions were needed to address the concerns and misconceptions of CCTs among PCPs. Findings from another study on enrollment into Phase III clinical trials suggested that gauging provider interest was important to patient accrual since providers were often less likely to actively recruit patients if they deemed a trial disinteresting or a significant deviation from their usual practices [87]. It could also be that the doctors face greater responsibility when putting a patient through CCT and they may not want to go down that route. Ethical concerns related to recruiting patients onto cancer clinical trials could also come into play when providers were concerned about the patient's increased vulnerability near the end of life and decreased capacity to consent [88].

Sometimes physician's reluctance in referring patients to CCTs stems from a fear of losing patients to other care providers. One study reported that fear of losing patients was associated with all referral behaviors among the physicians; however, this concern was more apparent among physicians from practices with lower levels of accreditation than those from practices with higher levels of accreditation [89]. The study concluded that in order to alleviate these fears, creative solutions must be identified and appropriately implemented to incentivize providers who feared the loss of patients after referral to clinical trials.

Another factor relevant for physicians' willingness to refer patients to CCTs lies in physicians' perceived burden of the clinical trial process. This issue is often referred to as "gate keeping" when providers label research as burdensome or upsetting [88]. One study reported that the burden associated with the clinical trial process was the only significant dimension associated with referring patients to early-phase clinical trials [82]. It was also found that physicians who felt burdened with logistical barriers, such as diverting time and resources away from their practice, were less likely to refer patients than physicians with opposing opinions.

3) Providers' ability to participate in CCTs

A provider's qualifications for and experience in conducting CCTs can have a direct impact on the chance of the provider's patients participating in a trial. There is evidence that accrual to CCTs was enhanced when the provider was a Principal Investigator [75,86]. It was also revealed that a provider's duration of practice was positively associated with patients' chance of accrual to CCTs, that is, the longer the provider worked at an institution, the more likely his or her patients would get enrolled into a CCT [75]. Providers with non-oncology medical specialties were less successful in patient accrual relative to those who specialized in oncology [86]. Even within oncologists, there is evidence that medical oncologists were more likely than surgical or radiation oncologists to discuss the possibility, benefits, and risks of clinical trial enrollment with their patients [89,90]. There remains a need for more oncologists to discuss CCTs with their patients to increase awareness and subsequently, enrollment [91].

The provider's experience in recruiting patients also matters. One study assessed the importance of consenter characteristics in patients' willingness in CCT participation [92]. It was found that cancer patients' willingness in clinical research participation was positively associated with consenters' experience. Another interesting finding from the same study was that gender discordances between consenters and patients were associated with a higher level of willingness to participate in clinical research by patients. Moreover, there is no standardized system to accrue patients onto CCTs. Thus better resources need to be developed so providers can identify eligible patients [91].

Physicians' capacity in referring patients to CCTs is constrained by the time they have and their practice locations. Based on data collected from 706 oncologists in the U.S., Kaplan et al. [89] reported that oncologists who spent most of their time in patient care were the least likely to discuss clinical trials with their patients. Specifically, in safety-net institutions, providers often face time-constraints, classifying research patients as an additional time burden [81].

C. Influence of provider-patient communication on CCT participation

Physicians act as gatekeepers and can influence a patient's awareness of as well as decisions to participate in a clinical trial [82,85]. Whether, when, and how physicians communicate with patients over CCTs can make a critical difference in the chance for patients to participate in CCTs. Recruiting patients into a clinical trial can be a delicate issue and intellectually and emotionally challenging for care providers, underscoring the need of proper training of care providers before they can effectively communicate with patients for potential CCT participation [93].

Effective communication between care providers and patients is important for reducing cancer fatalism or distrust in medical professionals among patients, especially among racial and ethnic minority patients with prevalent cancer fatalism and distrust [47,49,63,94]. Hong and You [95] reported significant trust differences in physicians among men who did

or did not experience uncertainty about the prostate-specific antigen (PSA) test during doctor-patient communication. Patients who experienced uncertainty about the PSA test were more likely than those without such experiences of uncertainty to place their trust in doctors. It was also found that patients who positively evaluated their interaction with doctors were less likely to report fatalistic beliefs about cancer. The study concluded that patients' communications with their care providers could influence patients' fatalistic beliefs and levels of trust in their medical doctors.

There is evidence that relative to White patients, racial and ethnic minority patients might receive less information about clinical trials in their communication with oncologists. One study Eggly et al. [96] assessed differences in oncologist-patient communication during offers to participate in clinical trials in oncology visits with African American and White patients. The results suggested that visits with African American patients, compared to visits with White patients, were shorter overall and included fewer mentions and less discussion of clinical trials. Meanwhile, the subjective beliefs and potential biases on the provider side can impact whom the providers communicate to about clinical trials, as providers may not approach patients they consider may be difficult to enroll or accommodate or less unlikely to accept [97].

Barriers in language and health literacy can pose a challenge to effective patient-provider communications for CCT accrual. Based on interviews with 111 oncologists in Texas, one study Ramirez et al. [82] found that 83% of the oncologists did not speak Spanish well enough or at all to interview patients despite the fact that 33% of the oncologists served Hispanic patients. A major recommendation from this study was to create bilingual study teams to solve language barriers and enhance the ability of Spanish-speaking patients to participate in clinical trials. Developing culturally-specific, bilingual cancer education and information helped to increase recruitment of Hispanic patients in CCTs [98]. Another study found that training medical interpreters for cancer patients with limited English proficiency increased the mean accuracy from 49% to 72% in knowledge test about cancer [99]. Having face-to-face communications with physicians and direct mailing of clinical trial information to patients was also found to help with recruiting African American patients into CCTs [29].

D. Contextual factors affecting CCT participation

A major contextual factor related to patient accrual to CCTs concerns the uneven distribution of CCTs in the U.S. Most clinical trials are conducted at research institutions such as National Cancer Institute (NCI) designated cancer centers and teaching hospitals [89]. One study reported that physicians who were involved in teaching or affiliated with a Community Clinical Oncology Program (CCOP) and/or an NCI-designated cancer center were more likely to participate in CCTs and enrolling patients [90]. Since teaching hospitals and NCI designated cancer centers are usually concentrated in major metropolitan areas, the chance for CCT participation among rural patients and healthcare providers becomes much lower [68,100]. Relative to their counterparts who practiced at NCI designated cancer centers and teaching hospitals, physicians with practices from community hospitals and non-accredited settings were more likely to perceive lack of information of CCTs as a major barrier [89].

Organizational contextual factors such as the infrastructure for implementing CCTs and organizational culture are also important in determining physicians' motivation for and success in recruiting patients [81,101]. Based on data collected from 481 physicians who were involved in NCI sponsored CCTs in 2011, one study found that physicians who practiced in programs that had more supportive policies and practices in place to encourage enrollment such as training, administrative support to screen and enroll patients, allocating incentives to enroll patients, and so forth, were able to enroll more patients [86]. This study also found that programs that mandated expectations for enrollment were more successful inpatient accrual because of a strong sense of organizational commitment and social norms.

Data collected from another study supported the need for a culture change among care providers to enhance clinical trial infrastructure at the organizational level [102]. Recognizing language barriers as an issue in recruiting some patients into cancer clinical trials, one study highlighted the need for cancer care organizations to become more health literate [103]. Similarly, the Agency for Healthcare Research and Quality (AHRQ) purported language competency and outreach efforts as necessary elements to create health literate organizations [104].

Whether a physician can have the needed administrative and institutional support for CCT referrals can also make a difference in patient accrual. Based on an evaluation of enrollment data from CCTs sponsored by the National Cancer Institute (NCI), one study identified organizational factors associated with patient accrual among participating healthcare organizations [86]. Findings from this study revealed that physicians' participation in CCTs became more likely when organizations were providing support for physicians to consent and enroll patients, offered incentives for enrollment, and mandated expectations for enrollment. Institutional structures such as organizational climate and research specific resources also play a role in providers' ability to recruit patients onto cancer clinical trials [81]. Oncologists who believed that research nurses and coordinators were helpful in supporting trial enrollment were more successful in clinical trial accrual [80].

Effective accrual of patients into CCTs often requires close communications between PCPs who want to refer their patients and oncologists who run clinical trials. Based on qualitative data from 27 PCPs, one study found that the strength of the relationship between PCPs and specialists played an important role in determining the likelihood of referrals [70]. PCPs usually send patients to specialists with whom they previously collaborated or whom they trusted. The study concluded that steps must be taken to strengthen communication between oncologists and referring PCPs to facilitate patient referrals by PCPs.

There is a well-documented need for community-based efforts in CCT recruitment [105]. CCT education was most effective when it was delivered through a peer-to-peer mode [106]. This usually requires training community leaders and

ambassadors on CCTs who can then convey the messages to their community members in a culturally relevant manner [107]. Training community members to share information of CCTs to their community allows for effective dissemination of materials, leading to more active interest from these communities [107]. Community health workers (CHWs) serve as an increasingly important bridge connecting underserved communities and the healthcare system, and they can be trained to promote CCT education and patient accrual in underserved communities [108,109].

Study Limitations

Two limitations of our study merit comments. First, due to the vast body of literature on CCT participation, our review of the literature focused on more recent studies on CCT participation in the U.S. published between 2008 and 2017. As a result, relevant findings from studies focusing on CCT participation in non-U.S. populations or published before 2008 were not included in our review of the literature. Second, we did not differentiate between therapeutic and non-therapeutic trials in our discussion of CCT participation. It is likely that some of the factors we reviewed might have differential associations with CCT participation depending on whether the trial is therapeutic or not. For example, because of clinical ethics physicians might feel more obligated to refer their patients to a therapeutic trial than to a non therapeutic trial whose benefit to the patients is not as clear [110].

Discussion

Borrowing insights from Coale's three preconditions for fertility decline, this study illustrates how the Ready-Willing-Able framework can help explain and streamline factors related to patient accrual to CCTs based on a review of recent literature. The findings suggest that a host of factors at various levels can individually impact the readiness, willingness, or capacity for CCT participation amongst both patients and healthcare providers. Meanwhile, the readiness, willingness, and capacity for CCT participation on either the patient or provider side can further influence and be influenced by patient-provider communications before the patient makes his or her decision over CCT participation. It is also important to note that the three aspects of CCT participation on both the patient and provider sides are constrained by contextual factors at the regional, healthcare system, organizational, and community levels that can determine not only the availability and distribution of CCTs, but also whether and the extent to which the infrastructure and organizational support for CCT implementation are in place.

The weakest link principle of the RWA framework [20] suggests that there might be different key deterrents for different groups of patients or healthcare providers that have prohibited them from being ready, willing, or able to participate in CCTs. For example, for patients or providers who live in rural or medically underserved areas where no or few clinical trials can be found, it would be very challenging, if not impossible, for them to be 'ready' for something nonexistent or they have not heard of. An examination of all public- and privately-funded phase II/III cancer clinical trials launched in the U.S. between 2008 and 2015 suggested increased inequality in the geographic distribution of CCTs over time- about 19% of trials were concentrated in only 1% of the hospital service areas in 2008 and by 2015 the same 1% of the health service areas hosted 25% of the trials [111]. Thus addressing this disparity becomes important for patients and providers from areas with a short supply of CCTs to gain better access to and readiness for participation.

Besides readiness, contextual factors also directly impact the willingness and capacity of both patients and providers to participate in CCTs. Of particular importance is the need to improve the organizational infrastructure to better support patient accrual and retention in CCTs, provide more training to providers, develop a practical referral system for CCT participation, and build trustful partnerships with local communities, especially with minority and underserved communities. Implementing a system to aid investigators in planning and establishing targets for accrual can facilitate the recruitment of minority cancer patients into trials [112].These steps and investments require long-term commitment and strategies that are usually not feasible with the temporal or cyclical nature of grant-funded clinical trials and limited budgets; however, these investments are needed and will pay off in the long-run when both the providers and a diverse body of eligible patients can be better supported and motivated to participate in CCTs.

Interventions aimed at promoting CCT participation also need to be tailored to address the unique barriers across different racial and ethnic groups, especially in consideration of the documented disparities in misconceptions and cancer fatalism associated with CCT participation across these groups [32,43,47-49]. Additionally, the channels patients turn to for information on clinical trials also varied by ethnicity. There was evidence that relative to Whites, Blacks and Hispanics were more likely to look to their churches for clinical trial information; whereas Whites were more likely to seek information from a doctor or the Internet [62]. Studies on perceptions of clinical trials among racial and ethnic minorities have consistently shown the importance of developing culturally specific assessments for these perceptions and tailoring educational strategies to correct misconceptions [113,114].

In light of the multitude of factors relevant for CCT participation, an integrated approach to promoting CCT participation and implementation should be considered. Consumer-based iterative approaches were found to be informative and successful in recruiting patients [115]. The gist of this approach lies in mobilizing needed resources, support, and endorsement from key stakeholders including, but are not limited to, patients, healthcare providers, communities, policymakers, and researchers to develop and implement targeted and concerted strategies to address specific barriers for CCT participation. Several studies have demonstrated the advantages of educating the general populace in the knowledge of cancer, cancer treatment, cancer research studies, and the intent to participate in cancer research [116,117]. One pilot study examined the effectiveness of lay navigators and found 95% of navigated patients consented to participate in a clinical trial. These navigated patients also had improved understanding of

clinical trials [118]. Based on the principles of Community-Based Participatory Research (CBPR), clinical trials need to better involve communities in the whole process, from trial design to implementation to dissemination of results [119].

Although barriers to CCT participation have been extensively studied, the rate of trial participation has not improved substantially over time [120]. Besides, minority patients in general and patients who are uninsured and underinsured, having lower socioeconomic status, or living in underserved or rural areas, are still underrepresented in CCTs [112]. Cost-effective use of technology can facilitate direct-to-consumer communication and patient accrual to CCTs. Adoption of centralized information technology such as the use of software to match trials to special populations can increase the efficiency of patient accrual [121]. Web-based decision aid can help improve patients' knowledge, self-efficacy, and certainty about choice, which can support informed decisions about trial participation among cancer patients [122]. Similar findings were also reported in other studies where innovative use of educational videos or internet-based strategies were proven effective in recruiting patients [112,123-127]. These strategies will become even more feasible with the increasing availability of internet access, use of smart phones, as well as the reduced cost of data storage and transfer over time.

Acknowledgements

We would like to thank Jessica Wiens and Grace Cai for their proofreading and editorial assistance to the manuscript.

Declaration of Interest Statement

The authors declare no financial or other conflict of interest.

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Received date: April 19, 2019; **Accepted date:** May 28, 2019; **Published date:** May 29, 2019

Citation: Su D, Ramesh S, Qu J, Farazi PA, Wang H, Siahpush M (2019) Ready, Willing and Able to Participate in Cancer Clinical Trials: Insights from a Theory on Fertility Transition. *J Health Sci Educ* 3(2): 158.