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Stepwise development of a cancer care delivery research study to evaluate the prevalence of virus infections in cancer patients

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Background: SWOG initiated a cancer care delivery research study of virus infection rates among newly diagnosed cancer patients. This study will inform viral screening guidelines in oncology clinics. **Methods:** In a first step 'vanguard' phase, we evaluated the feasibility of multiple study procedures. Site investigators were surveyed to obtain feedback on study implementation. **Results:** Much higher enrollment occurred at sites where all physicians participated and viral testing was performed as routine practice. These procedures will be required going forward. Additional protocol changes based on site investigator input were implemented. **Conclusion:** This multistep protocol design process illustrates how cancer care delivery research studies can adapt to real-world strategies and procedures that exist at community clinics where the predominance of cancer patients are treated.

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The field of cancer care delivery research (CCDR) is rapidly evolving and growing within the research portfolio of the National Cancer Institute (NCI) [1]. One emphasis in CCDR is to build the evidence base for how clinical practices and organizational processes and policies improve patient outcomes in the real world [2]. In this context, CCDR studies utilize and share characteristics of comparative effectiveness studies, which aim to provide study results that can be more confidently applied to a real world population. CCDR studies are more likely to be conducted in community clinics, and will be most successful if they can account for practice heterogeneity in their designs [3]. These studies may also be more complex – and will require more detailed healthcare information – than standard treatment trials. Therefore, giving community partners a voice in CCDR trial design and

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logistics may improve the chances of success in enrollment and follow-up.

SWOG, a member of the NCI's National Clinical Trials Network and the NCI Community Oncology Research Program, in concert with the Hutchinson Institute for Cancer Outcomes Research, recently embarked on a study to evaluate the prevalence of HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV) among newly diagnosed cancer patients in community oncology practices. To ensure that the design was feasible and acceptable to clinics with limited experience with CCDR studies, our strategy was to pilot test the study procedures within a selected sample of community clinics in a first step 'vanguard' phase. We then modified the final design of the study based on feedback from clinics. This report presents the original study design, the conduct of the vanguard phase, and the study modifications implemented based on the results of the vanguard analysis. These findings may be of interest to investigators conducting novel cancer care delivery research in community settings.

• Study rationale

SWOG S1204, 'A sero-epidemiologic survey and cost-effectiveness study of screening for human immunodeficiency virus, hepatitis B virus and hepatitis C virus among newly diagnosed cancer patients', was motivated by the recognition that immunosuppressive cancer therapy could produce severe adverse outcomes in patients who harbor latent viral infections. The prevalence of these infections among cancer patients may be rising. Given the effectiveness of modern antiviral therapies, persons with HIV will live much longer; 26% of prevalent HIV cases are now in those 55 years or older [4]. Most cancer survivors (60%) have never had an HIV test, and HIV testing rates decline sharply with age, even as cancer incidence increases [5,6]. Many viral infection cases will go undetected since patients can be symptom-free for an extended period [7,8]. Studies have documented fulminant liver failure among patients for whom latent HBV virus was reactivated during chemotherapy, including in cases where modern targeted therapies were used [9–11]. Acute reactivation of HCV following chemotherapy has been documented [12]. The rates of viral prevalence among those with cancer are largely unknown.

Screening guidelines for HIV, HBV and HCV are variable. Widespread screening for

HIV in the general population has been called for [13–15]. The CDC recommends routine screening for HBV for all patients undergoing chemotherapy, whereas the American Society for Clinical Oncology recommends risk-adaptive screening based on HBV infection risk or risk of HBV reactivation from anticipated cancer therapy [16,17]. The CDC and the US Preventive Services Task Force recommend HCV screening for those born from 1945 to 1965 and for those at increased risk, but not for the general population and not specifically for those receiving chemotherapy [8,18–19].

Methods

• Original study design

The primary objective of study S1204 (ClinicalTrials.gov Identifier: NCT01946516) is to estimate the prevalence of HIV, HBV and HCV infection among newly diagnosed cancer patients. Secondary objectives include evaluating whether prevalence rates vary by sociodemographic, clinical and behavioral factors, and evaluating the cost-effectiveness of routine screening for these viruses. The target enrollment is 3000 patients. The study was conducted after appropriate approval by individual institutional review boards of participating sites, in compliance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

To ensure that the study population represents the population of newly diagnosed cancer patients, exclusion criteria were limited. Patients ≥ 18 years old presenting for evaluation or treatment of a new, pathologically confirmed cancer malignancy (including hematologic) were eligible, including those seeking a second opinion. Testing for HIV, HBV and HCV was performed prior to registration. Patients who had HIV, HBV and/or HCV testing within 60 days prior to registration and did not wish to be retested were eligible if viral test results for all three viruses were submitted. Patients with pre-existing HIV, HBV and/or HCV who did not wish to be retested for those particular viruses were also eligible if documentation of viral status was submitted within 120 days prior to registration. Submission of blood samples for future research was optional. Patients with prior cancers within the past 5 years were ineligible, with the exception of basal cell or squamous cell skin cancer or cervical or breast carcinoma *in situ*. Sites must agree to ask all newly diagnosed, eligible cancer patients to participate. However, only

consenting patients were actually registered. Viral risk status is obtained at baseline using a patient-reported outcome measure (a 'viral risk survey'). Follow-up information at 6 months on treatments for cancer and viral infection is collected from medical records review for patients positive for any of the three viruses. All patients are followed for vital status for 5 years. The results for the main portion of this trial are anticipated to be published in 2017.

• Design & data collection for the study vanguard phase

The goal of the vanguard phase was to evaluate the feasibility of following the recruitment procedures and to implement modifications to the protocol to facilitate the study's successful completion. The two prespecified objectives were to estimate the proportion of screened patients who enrolled in the study and to evaluate the submission rates and completeness of baseline forms. We collected de-identified aggregate data monthly about all new cancer patients screened for the study at each site and who were assessed as potentially meeting the eligibility criteria specified above. This approach allowed estimation of the denominator of potentially eligible patients, thereby providing an estimate of the ratio of screened patients who enrolled. The study design considered a ratio of <0.50 to indicate a serious problem with the study design and/or eligibility. Also, patient demographics (age, sex, self-reported race and ethnicity, and cancer type) were collected to assess generalizability of the registered cohort.

We examined two issues in particular. Prior to study activation, sites expressed concern that routine screening of viral infections would not be supported by all their physicians. Similarly, some sites expressed concern that viral screening as routine practice was not appropriate for their site. Therefore, sites were allowed to decide whether to require all their physicians to participate and whether to require viral screening as routine practice at the site at their own discretion. The resulting variations in site procedures provided implicit 'control' groups for the different approaches, allowing comparisons between the different approaches within the context of the vanguard phase itself.

Throughout the vanguard period, monthly phone calls and email contact were maintained between study leadership and site staff to address issues with study procedures. At vanguard phase completion, members from each site were asked

to complete an exit survey, which included questions about preexisting clinic policies for viral risk assessment and testing, concerns about study implementation and conduct, and willingness to continue participation (see [Supplementary Material](#), exit survey design). Five sites participated in telephone interviews regarding the collection of the aggregate patient data. The study leadership used this input to identify additional analysis items.

The vanguard enrollment period ran from October 2013 to July 2014. Seven sites participated, with each site enrolling patients for approximately 3 months. Exit interviews were completed by 26 investigators from participating sites, including six head clinical research associates, six physicians and 14 with other (unspecified) study roles. Exit interview surveys were received from multiple investigators at each participating site (site level response rate = 100%).

All differences in patient characteristics and study participation rates were tested using chi-square tests.

Results

• Representativeness of the registered cohort

In total, 953 patients were screened and 312 were registered to the vanguard phase. Registered patients did not differ from nonregistered patients with respect to sex, race and type of cancer ([Table 1](#)). Registered patients were younger and more likely to be Hispanic.

• Study participation rate

The overall study participation rate was 33% (312/953; range: 7–67% by site). Sites with full physician participation had higher enrollment of screened patients (50 vs 24%; $p < 0.001$), and sites that included viral screening as routine practice also had higher enrollment rates (54 vs 26%; $p < 0.001$). Importantly, the impact of requiring viral screening as routine practice was additive with respect to physician participation ([Table 2](#)).

In a busy clinic environment, these differences are likely due to the difficulty of selectively tracking and offering study participation to screened patients. Going forward, the study requires full physician participation and viral testing as routine practice.

• Consent for viral testing

Two of the seven vanguard sites required written consent for HIV testing, and one site required Medicare patients to sign a financial waiver for

Table 1. Demographic and cancer characteristics.

Characteristics	Total screened [†] (n = 953), n (%)	Registered (n = 312), n (%)	Not registered (n = 641), n (%)
Gender:			
– Male	322 (34)	103 (33)	219 (34)
– Female	631 (66)	209 (67)	422 (66)
Race:			
– White	658 (76)	228 (77)	430 (75)
– African–American	164 (19)	52 (17)	112 (20)
– Asian	37 (4)	14 (5)	23 (4)
– Other	9 (1)	4 (1)	5 (1)
– Unknown	85	14	71
Ethnicity[‡]:			
– Hispanic	145 (16)	84 (27)	61 (10)
– Not Hispanic	749 (84)	228 (73)	521 (90)
– Unknown	59	0	59
Age[‡]:			
– <50 years	169 (18)	82 (26)	87 (14)
– 50–59 years	249 (27)	93 (30)	156 (25)
– ≥60 years	506 (55)	137 (44)	369 (60)
– Unknown	29	0	29
Cancer types:			
– Breast	338 (35)	106 (34)	232 (36)
– Colon/colorectal	96 (10)	38 (12)	58 (9)
– Lung	100 (10)	31 (10)	69 (11)
– Prostate	18 (2)	1 (0)	17 (3)
– Other	401 (36)	136 (33)	265 (37)

[†]Indicates screened for study participation and potentially eligible.
[‡]Statistically significant difference between patients registered versus not registered, $p \leq 0.05$.

HIV testing. The observed study participation rate was slightly higher (35%) in sites that imposed any form of additional written consent compared with sites that did not (32%). Thus there was no evidence that more rigorous consenting efforts for HIV were associated with lower study participation (Table 3). No clinic required consent prior to HBV or HCV testing.

• Baseline data submission rates

The rate of form submission was 100% for the study's baseline forms (a prestudy information form and a viral status form) and 99% for the viral risk survey. The item response rate for submitted questionnaires was 95% on the viral risk survey. Thus, data submission and completeness for the baseline forms was excellent.

• Patient screening

The effort to track and profile screened patients in order to establish a denominator was resource intensive; representative feedback from exit interviews included reports that 'keeping the monthly summary report was time consuming' and 'it is a

huge time commitment' (Table 3). Sites reported that 1 h was required, on average, to track and collect data for each screened patient. To help mitigate this burden, sites were provided a study-specific tracking tool in the form of an Excel spreadsheet.

• Registration timing

The original design envisioned obtaining consent for study participation from the patient at their first clinic visit. In the exit surveys, most sites indicated that approaching patients at their first visit was often 'difficult', since this was a 'distressing and overwhelming' time for patients just learning about the extent of their diagnosis (Table 3). In this setting, participation rates would likely also be lower, as patients would be more likely to decline.

Based on these results, we relaxed the eligibility criterion, requiring instead that sites enroll patients at any time within 90 days after their initial visit to the site. Within this 90-day period, patients were required to complete their consent, viral testing, viral risk survey and (optional) blood sample submission.

- **Pathology documentation**

The original design required documentation of the pathology diagnosis of each patient's cancer to confirm eligibility. This requirement is typical for treatment trials, wherein the study sample must be strictly ascertained to establish a valid estimate of the treatment effect in a limited, homogeneous population [20]. Some sites indicated that not all eligible cancer types were readily amenable to pathologic diagnosis (e.g., hepatocellular carcinoma diagnosed under Organ Procurement and Transplantation Network criteria). To emphasize the inclusion of a broad range of cancers, eligibility was modified. Sites are now required to assert that evidence of the diagnosis exists in the patient medical record.

- **Blood sample collection**

The collection of blood samples for repository storage and secondary analyses was of great interest. All sites were initially required to offer patients the opportunity to consent to submit blood samples, required to be stored in -70 to -80°C freezers prior to shipping to the central repository. However some sites – especially smaller community oncology clinics – indicated such freezers were not available. We modified the study, allowing optional site-level participation in blood sample collection. Although this approach will limit the number of blood samples collected (as well as the breadth of institutions collecting samples), it will also allow us to include a broader cross-section of sites. In this trade-off, we emphasized improving the

generalizability of the primary study objective – estimation of viral infection prevalence rates – over the secondary end points related to sample collection.

- **Language barriers**

Study forms were initially provided in English only, but most sites (6/7) indicated in their exit survey responses that language barriers were a concern for many patients, particularly Spanish-speaking patient populations (Table 3). With the study revision, the viral risk survey and consent were provided in Spanish. Translations into other languages will be supported at the site level.

- **Patients without health insurance**

In the vanguard phase, a temporary fund in the amount of US\$10,000 was established to cover potential viral testing costs for patients without health insurance. However, the funds were never used during the vanguard phase. This fund has been discontinued for the remainder of the study.

- **Study accrual timeline**

The addition of a vanguard phase allowed us to better estimate the time to full accrual. Under the revised protocol, the study is projected to take 2.25 years to complete full accrual with the same set of participating institutions (or 1.5 years with a 50% increase in site participation). Better estimation of accrual duration allows study leadership to more accurately assess budgetary implications.

Table 2. Study participation rate.

Site characteristics	Patients registered (n)	Patients screened but not registered [†] (n)	Patients screened (n)	Study participation rate [‡] (%)
All physicians participated:				
– No	148	474	622	24
– Yes	164	167	331	50
Viral testing was routine practice:				
– No	186	532	718	26
– Yes	126	109	235	54
All physicians participated:				
– No	148	474	622	24
– Yes	38	58	96	40
– Yes	126	109	235	54
Total	312	641	953	33

All differences between registered patients and patients screened but not registered were highly statistically significant ($p < 0.001$).

[†]Indicates screened for study participation and potentially eligible.

[‡]Study participation rate equals the number of patients registered (numerator) divided by the total number of patients screened (denominator).

Table 3. Representative site exit survey responses for selected questionnaire items.

Site No.	Consent for viral testing	Patient screening	Registration timing	Language barriers	Viral testing reimbursement and insurance denials	Willingness to continue to main study
1	We changed our clinic policy of viral testing only patients who were going to receive chemotherapy to all new cancer patients. Since we let patients know this is our new policy most patients comply with testing	Keeping the monthly summary report is time consuming specially if the study is open for months, these logs ask for a lot of information	I delayed approaching some patients at their very first visit. Finding out the cancer diagnosis and all other information was usually distressing and overwhelming for patients	Having Spanish consent and viral risk survey would help immensely, especially for hospitals like us which serve a huge Spanish-speaking population	No comments were provided	Respondent 1: Yes, I believe this is the future standard and the practice benefits patients Respondent 2: Yes, we would participate. It was a relatively easy study to recruit for, not too laborious in terms of data and case report forms. Testing all new patients for viral tests was a good standard for our hospital given it is a safety net hospital which serves low income families, minorities and uninsured. Some of these patients rarely get tested for these viral diseases otherwise
2	[Viral testing is] primarily doctor based. Some ordered viral testing as a standard, others did not. We have been trying to make it standard across the board for a while now	The study is very taxing on the clinical trials offices mainly due to the management of all newly diagnosed patients, which not only involves seeing if they had viral testing done or not but also finding the ideal time to approach the patient whether or not it actually was in the oncology clinic	We also decided to not approach until after the first visit [when the] diagnosis and treatment plan is first discussed with a patient	Language was a barrier (getting a Spanish consent/qualify of life [form] would help significantly)	No comments were provided	Yes, it is an important study question and I felt like our site was slowly mastering the intricacies of this high throughput study. Just as the vanguard-phase ended was when we had the most clinic buy-in and support for the study
3	There is an HIV-specific consent form that needs to be signed by both the patient and physician, documenting the date and time the consent form was signed	No comments were provided	Initial visits sometimes were difficult due to patient being overwhelmed Yes, we would try to do at next visit if possible	Our patient population has a large number of Spanish-speaking individuals and there was a delay in getting the consent form, viral risk survey, among others. translated into Spanish. Once the documents were translated this was no longer a concern	No comments were provided	Yes – although it took a while for our site to coordinate with the whole team and figure out the logistics, after several team meetings we were able to organize our approach and the study ran smoothly

Table 3. Representative site exit survey responses for selected questionnaire items (cont.).

Site No.	Consent for viral testing	Patient screening	Registration timing	Language barriers	Viral testing reimbursement and insurance denials	Willingness to continue to main study
4	<p>Respondent 1: We do have a form that lets patients know that HIV status is being evaluated</p> <p>Respondent 2: Patients consent to this testing as a new patient. It is included in our general consent for treatment</p> <p>Respondent 3: No problem with patient acceptance (of viral testing)</p>	<p>Respondent 1: We would have to limit the study to perhaps one site because truly the time involved per day for this trial for one staff member was sometimes greater than 4 h</p> <p>Respondent 2: Often the chart information is not accurate and complete until after the initial visit; our staff kept lists upon lists and updated the outcome of the patient frequently, i.e., diagnosis as well as next appointment</p>	<p>In most cases the patient was approached by a research staff member at the second visit; the first visit can be extremely overwhelming; this also allowed our staff to follow-up with patients seen and truly identify those with a cancer diagnosis</p>	<p>Spanish-only-speaking patients</p>	<p>We established a system that would allow research to assess the bill and pay at a predetermined research rate</p> <p>Some insurance issues. The routine testing for hepatitis prior to Rituxan® use has helped in this regard</p>	<p>No comments were provided</p>
5	<p>No comments were provided</p>	<p>No comments were provided</p>	<p>Respondent 1: A significant barrier to recruitment was the requirement for pathologic testing for hepatocellular carcinoma patients, a diagnosis that is confirmed radiologically and that often goes along with positive hepatitis testing</p> <p>Respondent 2: If they were overwhelmed and or they were having difficulty with the diagnosis and treatment option explanations and standard care, we delayed or deferred</p>	<p>We are required to have a translated International Classification of Diseases for our population, and only had English and Spanish, so missed Vietnamese and others</p>	<p>No comments were provided</p>	<p>Yes</p>

Table 3. Representative site exit survey responses for selected questionnaire items (cont.).

Site No.	Consent for viral testing	Patient screening	Registration timing	Language barriers	Viral testing reimbursement and insurance denials	Willingness to continue to main study
6	[The Institutional Review Board was] quite concerned regarding the confidentiality issues surrounding HIV testing	No comments were provided	If the patient was overwhelmed, the study and testing was discussed with them at subsequent visits		Medicare patients required to sign form stating that they understand that they may be responsible for the cost of testing if not covered by Medicare. This severely handicapped our ability to make viral testing the standard of care	I do not think the internal financial requirements make further participation feasible
7	No difficulty in testing	It is a huge time commitment (at least an hour a day). We have a very small research staff	Respondent 1: We were more successful in approaching patients a few weeks after presentation of new diagnosis so they had dealt with stress of diagnosis but still many patients declined Respondent 2: 80% of the time patients were not approachable during the first visit. They were receiving way too much information relating to their cancer diagnosis	Language barrier could not be handled	No comments were provided	Respondent 1: It would be okay. It is not hard to explain the study to patients Respondent 2: No. It is a huge time commitment (at least an hour a day). We have a very small research staff

- **Viral testing reimbursement & insurance denials**

One concern voiced by many clinics was that insurance companies would not cover routine viral testing. In the follow-up survey, no site reported having ongoing issues with insurance denials of HIV, HBV or HCV tests. One site required Medicare patients to sign a form stating that they would be responsible for the cost of testing if not covered by Medicare; this site did not report any billing issues but site staff did attribute the low registration rate in part to this waiver requirement. No site reported that lack of insurance coverage prevented registration for any patients. Based on these results, it was suggested that sites could remove language in consent forms about possible insurance noncoverage. Also, viral testing windows were expanded to include any viral test results within 1 year prior to registration to better reflect general insurance payment schedules (Table 4).

- **Consent form**

The 12-page informed consent was modeled after a typical consent form for clinical trials. In the exit surveys, two sites indicated that at least one patient did not participate due to consent issues. One site commented that “the consent is lengthy due to regulatory issues and takes forever.” Based on the monthly summary data, consent issues were reported as reasons for nonparticipation for four total patients. Thus there were not substantial data indicating that the consent form was a major reason for nonparticipation.

Discussion

Cancer care delivery studies will comprise an increasing share of the cancer research portfolio. Here, we report on a preplanned vanguard phase for a prospective observational study designed to inform HIV, HBV and HCV screening policies for new cancer patients. This viral screening study offered unique challenges, necessitating a multistage protocol design process to test the anticipated procedures in nonresearch oriented clinical practice settings. Our overall goal with the vanguard phase was to implement study procedures that would produce generalizable results and would be feasible for sites, while maintaining the integrity of the study design. Input from the community sites was crucial. Overall the process was transformative to the study, as the vanguard phase provided rich data

to inform and improve the final protocol design. As such, our process may serve as a model for future studies in cancer care delivery.

One theme that emerged was that measures which allowed more patients to be eligible and increased generalizability of the primary end point also tended to reduce site staff and patient burden (Table 4). In addition, requirements that viral testing be implemented as routine practice within clinics, and that all physicians participate, will also increase generalizability by limiting selective viral testing of patients. The exclusion of sites that do not meet these criteria might induce a site-level bias, if such sites enroll a different type of cancer patient with respect to viral prevalence rates. However, since these sites are not implementing either of these procedures, the sites are likely also not adequately representing their own patient populations with respect to viral prevalence rates. In particular, patients who are more sick or more difficult to access – representing subpopulations of patients where viral prevalence rates are likely higher – would be less likely to be enrolled. Our greater concern was to include these subpopulations of patients to the greatest extent that was possible, so our assessment was that the better approach was to include only those sites that satisfied both of these requirements.

The final protocol will also emphasize the participation of community clinics which best reflect the general cancer treatment population. In classical efficacy trial designs, the introduction of heterogeneity in the study sample can reduce power and increase potential confounding, limiting internal validity and interpretation. In contrast, in this CCDR study, greater inclusiveness increases the likelihood that the viral infection prevalence estimates are externally valid.

Both *ad hoc* and structured feedback from site staff and physicians was crucial in generating the final revised protocol. The protocol development process was similar to other recent comparative effectiveness designs that rely on diverse input to identify critical issues and refine the protocol. Ramsey *et al.*, in their development of a large, randomized trial (RxPONDER) to evaluate the relevance of genetic testing in the assignment of appropriate therapy for breast cancer, relied on an external stakeholder group to inform study development [21]. Importantly, a protocol development approach that emphasizes collaboration between site investigators

Table 4. Summary of study design changes implemented based on evaluation of vanguard data.

Issue examined	Concern	Findings from vanguard	Final procedure
Physician participation	Routine screening of all patients would not be supported by all physicians	Sites with full physician participation had much higher study participation rates than those without (50 vs 24%)	All sites required to have full physician participation
Viral testing as routine practice	Viral testing as routine practice may be not considered appropriate for all sites	Sites where viral testing was routine practice had much higher study participation rates than other sites (54 vs 26%)	All sites required to implement viral testing as routine practice
Patient screening	Collection of aggregate monthly data would be time consuming	Average of 1.0 h per screened patient	Provide tracking tool and other assistance as needed
Language barriers	Forms in English only would limit participation for non-English speaking populations	Site reports that language barriers frequently experienced, especially Spanish	Provided the viral risk survey and the model informed consent in Spanish
Registration timing	Requirement that patients be consented and enrolled at first visit too strict	Routinely consenting and enrolling patients at first visit was problematic (e.g., frequent reports that patients were 'overwhelmed' at first visit)	Modified eligibility to require that patients be enrolled within 90 days after their initial visit
Pathology documentation	Requirement of documentation of pathologic diagnosis of cancer too strict for certain cancer types	Site reports that certain cancer types (i.e., hepatocellular carcinoma by OPTN) not readily amenable to pathology diagnosis	Eligibility modified to require only that sites assert that evidence of diagnosis exists in the patient medical record
Sample collection	Some sites may not have appropriate infrastructure to collect, store and submit blood samples	Not all vanguard sites reported having adequate freezer capability	Modified eligibility to make sample collection optional
Participation of indigent patients	Sites may be burdened with uncompensated costs for viral testing	A provisional fund established to cover the costs for indigent patients was never used	Discontinued provisional fund
Prestudy viral testing window	The original design required patients with HIV, HBV or HCV testing conducted >60 days prior to registration (or >120 days for viral positive patients) to be retested to meet baseline reporting requirements	Patients with viral test results conducted within 1 year prior to registration, but outside the specified prestudy window, would need to be retested. Sites expressed concern about insurance reimbursement for multiple viral tests within 1 year	Modified eligibility to allow prior viral testing results for HIV, HBV and HCV up to 1 year prior to registration for all patients

HBV: Hepatitis B virus; HCV: Hepatitis C virus; OPTN: Organ Procurement and Transplantation Network.

and the study leadership can provide a broad sense of ownership of the study and its findings. We note that six of the seven participating sites expressed interest in participating in the main study phase, despite some of the procedural difficulties inherent in the study design.

A limitation of the inclusion of a vanguard phase is a greater commitment of time and effort early in the study, from both the staff and physicians at the vanguard sites, and from the study leadership. However, it is anticipated that these early efforts will generate a protocol that accrues more rapidly and is better designed to meet the study objectives. Also, it is probable that the procedural hurdles faced by the limited number of vanguard sites are not wholly representative of those that will be encountered by the sites that will participate in the main trial, although we expect that major issues have been identified and mitigated. Screened patients who were not registered were less likely to be Hispanic. This issue will be monitored going forward. Finally, although necessary for establishing the representativeness of the registered sample within sites, the collection of monthly aggregate data to profile the screened cohort is time consuming for site staff.

Conclusion

Because this study promises to provide vital information that will inform viral screening guidelines for oncology clinics, we considered it essential to establish the early success of the study procedures. In this context, the prespecified study vanguard phase operates like an early stopping rule for protocol procedures, rather than study end points. Taken together, this multistep protocol design process illustrates how CCDR study designs can adapt to real-world strategies and procedures that exist at community clinics where the predominance of patients with cancer receive care.

Future perspective

Cancer care delivery research is a discipline which promises to grow substantially in the coming decades. One of its goals is to translate new cancer care policies, processes and procedures into community-based clinical practice. Accordingly, the development of research methods to allow appropriate inference about the effectiveness of new interventions in complex community practice settings will increasingly be required. The multistage protocol

design approach presented in this paper is one such method to help ensure feasible cancer care delivery research study designs.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <http://www.futuremedicine.com/doi/full/10.2217/fon-2015-0076>

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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EXECUTIVE SUMMARY

- The field of cancer care delivery research (CCDR) is growing rapidly within the research portfolio of the National Cancer Institute.
- A goal of CCDR studies is to examine how cancer care policies, processes and procedures impact real-world patient outcomes.
- Appropriate methods will be required to conduct CCDR studies within the potentially complex care settings of community-based clinics.
- Immunosuppressive cancer therapy can produce severe adverse outcomes in patients who harbor latent viral infections, and the prevalence of these infections among cancer patients may be rising.
- To ensure the feasibility of a study designed to evaluate the prevalence of HIV, hepatitis B virus, and hepatitis C virus in newly diagnosed cancer patients, we pilot tested the study procedures within a selected sample of community clinics in a first step 'vanguard' phase.

Methods

- Patients must have been 18 years or older and presenting for evaluation or treatment of a new cancer malignancy.
- Participating sites must have agreed to ask all newly diagnosed, eligible cancer patients to participate.
- The two prespecified objectives were to estimate the proportion of screened patients who enrolled in the study (the 'study participation rate') and to evaluate the submission rates and completeness of baseline forms.
- Additional protocol and logistical issues were also examined based on structured and *ad hoc* feedback from site investigators.

Results

- In total, seven sites participated in the vanguard phase; 953 patients were screened and 312 were registered, for an overall study participation rate of 33%.
- The study participation rate was much higher in sites with full physician participation (50 vs 24%; $p < 0.001$) and in sites that included viral screening as routine practice (54 vs 26%; $p < 0.001$).
- Based on this observation, going forward, the study will require full physician participation and viral testing as routine practice.
- Baseline data submission rates for required forms was excellent (>99%), as was the item response rate (95%).
- Multiple additional other protocol changes were enacted to enhance study feasibility.

Discussion

- Our overall goal with the vanguard phase was to implement study procedures that would produce generalizable results and would be feasible for sites, while maintaining the integrity of the study design.
- Input from site staff and physicians was crucial in generating the final revised protocol.
- Protocol changes which allowed more patients to be eligible and increased generalizability of the primary end point also tended to reduce site staff and patient burden.
- This study promises to provide vital information that will inform viral screening guidelines for oncology clinics.
- This multistep protocol design process illustrates how CCDR study designs can adapt to real-world strategies and procedures that exist at community clinics where the predominance of patients with cancer receive care.

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