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Feasibility of Cancer Clinical Trial Enrollment Goals Based on Cancer Incidence

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abstract

PURPOSE More than 20% of US clinical trials fail to accrue sufficiently. Our purpose was to provide a benchmark for better understanding clinical trial enrollment feasibility and to assess relative levels of competition for patients by cancer diagnosis.

METHODS The Database for Aggregate Analysis of ClinicalTrials.gov, up to date as of September 3, 2017, was used to identify actively recruiting, interventional oncology trials with US sites. Observational studies were excluded because not all are registered. Trials were categorized through Medical Subject Headings or free-text condition terms and sorted by cancer diagnosis. Trials that included more than one cancer diagnosis were included in the overall cohort but excluded when evaluating enrollment by cancer type. Trial enrollment slot availability was estimated between September 1, 2017, and August 31, 2018. Availability was estimated from total anticipated enrollment and duration, assuming a constant recruitment rate. Estimates for studies with both foreign and domestic sites were then prorated to calculate available enrollment in the United States alone. Ratios of the number of newly diagnosed patients in the United States available per trial slot were estimated using the American Cancer Society cancer incidence estimates for 2017.

RESULTS A total of 4,598 interventional oncology trials were identified. Overall, the estimated ratio of newly diagnosed patients available per trial slot was 12.6. Estimated ratios of patients per trial slot for six cancer diagnoses with the highest potential of 12-month US enrollment were as follows: colorectal, 24.7; lung and bronchus, 20.1; prostate, 17.6; breast (female), 13.8; leukemia, 11.6; and brain and other nervous system, 6.0.

CONCLUSION For all cancers, successfully accruing trials currently open would require that more than one in every 13 recently diagnosed patients (7.9%) enroll. This ratio and relative difficulty of accrual varies among cancers examined.

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INTRODUCTION

The premature termination of oncology clinical trials has been a longstanding issue, with failure to meet accrual goals being one of the many problems that plague unsuccessful trials.[1,2] On the basis of estimates from government, private, and academic sponsors, the overall rate of trial failure ranges from 20% to nearly 40%.[3-6]

With estimates of trial enrollment ranging from 2% to 8%,[7] there would appear to be many more patients available for trial enrollment. However, many trials are restricted to specific diagnoses, and no studies have examined the relationship between specific cancer diagnoses and trial openings per cancer diagnosis to understand the relative supply-and-demand characteristics. Given the lack of adequate enrollment in clinical trials, seeking effective means to manage trials and the finite pool of potential participants is critical. By using the information available at ClinicalTrials.gov through the Database for Aggregate Analysis of ClinicalTrials.gov (AACT),[8] we provide an estimate of the current number of oncology clinical trial openings compared with the incidence of various cancer diagnoses. We also provide an updated characterization of the clinical trial portfolio, building off prior analyses of ClinicalTrials.gov data.[9] With this information, we hope to enable further discussion on the state of national oncology clinical trials and prompt a deeper understanding of the current capability to meet trial accrual goals.

METHODS

Data Set Creation From ClincialTrials.gov

The portfolio of clinical trials was obtained from a static copy of AACT, up to date as of September 3, 2017. A total of 253,574 studies were downloaded. Studies not

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Can we provide an estimate of the current number of oncology clinical trial openings, in comparison with the incidence of various cancer diagnoses, to prompt a deeper understanding of the current capability to meet trial accrual goals?

Knowledge Generated

Our estimate indicates that approximately 8% of patients (ie, 1 in every 13) would need to enroll in clinical trials to meet accrual demands.

Relevance

It is important to investigate whether the failure of clinical trials to meet enrollment goals is due to an actual shortage of patients or other factors. Our findings may guide trialists and policymakers to bolster resources where incidence may be too low to support the current number of trials.

designated as interventional or observational were excluded as were those that did not have an overall status of recruiting. The data set was then restricted to studies that listed at least one study facility within the United States. This resulted in 19,214 studies that were then reviewed for relevance to oncology (Fig 1).

Coding of Disease Terms of Interest

The 2016 Medical Subject Headings (MeSH) thesaurus[10] was reviewed by three members of the study team, including an oncologist at the Duke Cancer Institute, to identify oncology-relevant terms. The MeSH thesaurus was filtered for terms that occurred in at least one or more of the studies in the data set, generating 7,413 total terms. These were compared with terms from the 2010 thesaurus previously reviewed by other investigators,[9] and a total of 6,176 matches were found. This left 1,237 novel terms from the 2016 thesaurus that were then coded as oncology relevant or nonrelevant and added to the existing list. Of the 7,413 MeSH terms, 1,061 were identified as relevant to oncology. In addition, 1,699 non-MeSH condition terms that occurred in 5 or more studies were also reviewed for oncology relevance, identifying 771 oncology terms.

Identification and Categorization of Oncology Trials

Relevant oncology trials (n = 5,906) were isolated from the subset of 19,214 trials and further categorized into 32 different cancer diagnoses using the disease condition terms (both MeSH and non-MeSH). A trial was assigned a particular cancer diagnosis if it had one or more terms that indicated that diagnosis. Trials were excluded if they had any problems with data quality (n = 488) or had an anticipated enrollment greater than 20,000 (n = 11) because they likely represented studies not focused on cancer treatment. These 11 trials are listed in Appendix Table A1. Data quality issues were defined as a missing start date, missing primary completion date, start date after the date of data download, primary completion date before the date of data download, start date later than the primary completion date, missing enrollment, enrollment tagged as "actual" not "anticipated", or primary completion date tagged as "actual" not "anticipated." Trials that covered more than one of the 32 diagnoses (N = 1,950) were included in the overall cohort for all cancers combined but were excluded when evaluating trials within individual diagnoses to avoid double-counting of available trial enrollment slots, which would reduce the reliability of the estimates.

Calculation of Estimated Available Enrollment Slots

Available enrollment was estimated on the basis of total anticipated enrollment and prorated to study duration, to date. This was then prorated to the proportion of study sites in the United States to provide an estimate of US-based enrollment. The start date of each study is reported on ClinicalTrials.gov, but the enrollment completion date is not. Hence, the date at which follow-up of the primary end point was completed was used as a surrogate measure. We were unable to track actual enrollment numbers because patient accrual metrics are not actively recorded on ClinicalTrials.gov and are only reported after trials complete enrollment. The following was calculated for each study where the expected enrollment over the next 12 months (or until completion if sooner): For studies ending $\geq$ 12 months from download date: = 12 (anticipated enrollment/anticipated total duration). For studies ending $<$ 12 months from download date: = anticipated remaining duration (anticipated enrollment/anticipated total duration). A multiplier calculated as No. of sites in the US/total No. of sites was used to prorate the enrollment metric to US sites only.

Characterization of Oncology Trial Data Set

For all oncology studies, the following characteristics were summarized: (1) funding source, (2) start year, (3) year of completion of follow-up for primary end point, (4) total planned enrollment, and (5) total planned duration, and study locations (United States only *v* United States and foreign). Interventional studies were further described on the basis of: (1) phase, (2) number of arms, (3) randomized

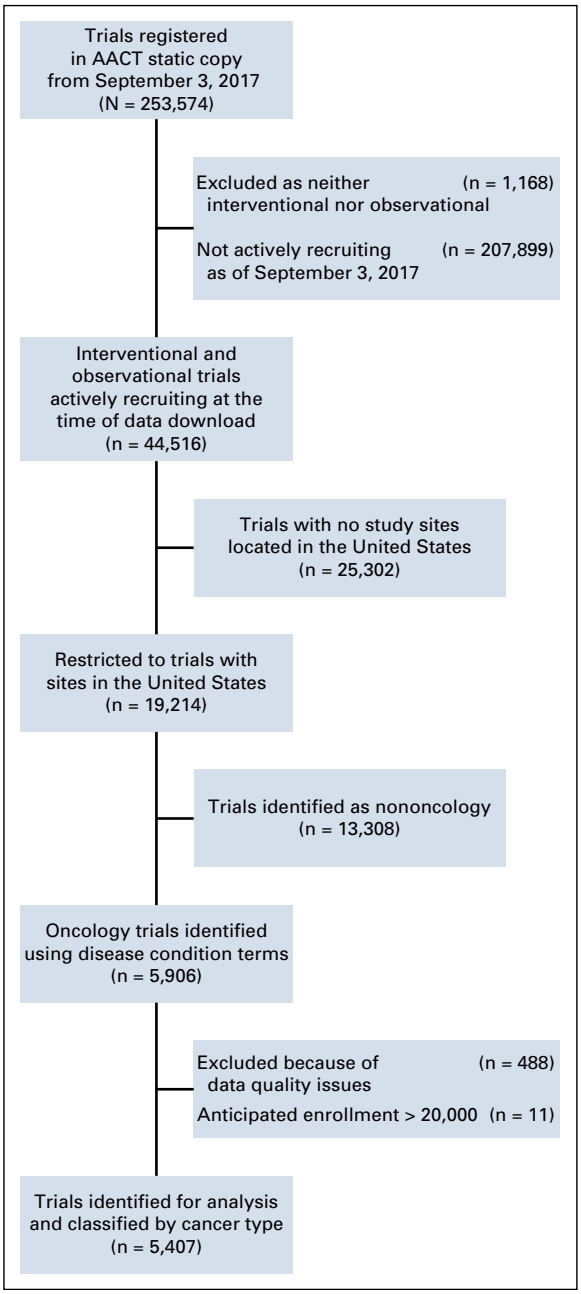

FIG 1. Studies reviewed for relevance to oncology. AACT, Database for Aggregate Analysis of ClinicalTrials.gov.

allocation, and (4) intervention type (ie, behavioral, device, or drug).

Study characteristics of the five most frequently studied cancer diagnoses were also described. Previously published American Cancer Society estimates of 2017 cancer incidence[11] for each diagnosis were then divided by the projected 12-month enrollment, prorated for US sites, for each diagnosis to generate a value that expresses the number of incident cases per clinical trial opening. We chose to only perform this particular comparison with interventional trials because these are the predominant trial type in the portfolio.

Statistical Analysis

The trials were characterized using descriptive statistics. The use of statistical inference was limited. Continuous variables were summarized with medians and percentiles (25th-75th), and binary and categorical variables were summarized with counts and percentages. Missing values were excluded from calculations of summary statistics. The Spearman rank correlation statistic was used to calculate correlation between the 2017 incidence across all cancer diagnoses and the projected 12-month enrollment and enrollment prorated for US sites. Calculations were performed using SAS 9.4 statistical software (SAS Institute, Cary, NC).

RESULTS

Distribution of Oncology Trials by Cancer Diagnosis

Of the 5,407 oncology-relevant trials that met inclusion criteria, 4,598 (85%) were interventional trials. Among these, female breast cancer was the most commonly studied diagnosis, encompassing 10% of all trials. Other frequently studied cancers were lung and bronchus (6.8%), prostate (6.1%), leukemia (6.0%), and brain and other nervous system (5.5%; Table 1). At total of 1,950 studies (36.1%) enrolled more than one diagnosis and were excluded from counts for specific cancers. Three hundred thirteen trials (5.8%) were not specific to any cancer diagnosis. Figure 2 shows the number of interventional trials by cancer diagnosis versus the respective estimated incidence. An average of 367 incident cases per trial was calculated as the ratio of total estimated incident cases in 2017 (n = 1,688,780) to number of interventional trials (n = 4,598).

Basic Characteristics of the Oncology Trial Portfolio

Among trials with at least one US site, the majority were funded by industry (38.7%) or other sources (38.3%), such as foundations, cooperative groups, or academic institutions (Table 2). A greater proportion of trials were single arm (55.8%). When examining only interventional studies, 72.3% included a drug intervention. Forty-three percent were funded by industry, and 22.5% received funding from the National Institutes of Health. Single-arm design was represented by 52.7%, and 73.3% were phase I or II type trials (n = 3,372). Only 28.1% were randomized. Trial characteristics for the top five most-studied cancer diagnoses are listed in Appendix Table A2. Attributes for observational trials are listed in Appendix Table A3.

Estimated Available Enrollment Slots by Cancer Diagnosis

The average total anticipated enrollment of all cancer trials was 311 patients per trial (standard deviation [SD], 1,143; median, 70; 25th-75th percentile, 36-175). On average, interventional trials had a total anticipated enrollment of 167 (SD, 589; median, 60). For interventional clinical trials, female breast cancer had the greatest number of estimated available enrollment slots for the next 12 months, prorated for US sites, with 18,294 (Table 3). Brain or other nervous

TABLE 1. Distribution of Studies by Cancer Diagnosis

Cancer Diagnosis[a]	Cancer Study Type, No. (%)		
	All (N = 5,407)	Interventional (n = 4,598)	Observational (n = 809)
Breast (female)	543 (10.0)	447 (9.7)	96 (11.9)
Lung and bronchus	367 (6.8)	314 (6.8)	53 (6.6)
Prostate	328 (6.1)	269 (5.9)	59 (7.3)
Leukemia	322 (6.0)	291 (6.3)	31 (3.8)
Brain and other nervous system	295 (5.5)	250 (5.4)	45 (5.6)
Myeloma	156 (2.9)	145 (3.2)	11 (1.4)
Pancreas	150 (2.8)	123 (2.7)	27 (3.3)
Melanoma of the skin	132 (2.4)	114 (2.5)	18 (2.2)
Sarcoma	128 (2.4)	109 (2.4)	19 (2.3)
Colorectum	127 (2.3)	101 (2.2)	26 (3.2)
Hepatobiliary	115 (2.1)	96 (2.1)	19 (2.3)
Urinary bladder	98 (1.8)	77 (1.7)	21 (2.6)
Ovary	86 (1.6)	76 (1.7)	10 (1.2)
Kidney and renal pelvis	73 (1.4)	64 (1.4)	9 (1.1)
Esophagus	37 (0.7)	27 (0.6)	10 (1.2)
Thyroid	34 (0.6)	32 (0.7)	2 (0.2)
Oral cavity and pharynx	30 (0.6)	25 (0.5)	5 (0.6)
Uterine corpus	25 (0.5)	23 (0.5)	2 (0.2)
Uterine cervix	25 (0.5)	21 (0.5)	4 (0.5)
Other endocrine	25 (0.5)	20 (0.4)	5 (0.6)
Stomach	13 (0.2)	10 (0.2)	3 (0.4)
Anus	10 (0.2)	10 (0.2)	0 (0.0)
Non-Hodgkin lymphoma	8 (0.1)	5 (0.1)	3 (0.4)
Eye	6 (0.1)	5 (0.1)	1 (0.1)
Larynx	4 (0.1)	4 (0.1)	0 (0.0)
Hodgkin lymphoma	3 (0.1)	2 (0.0)	1 (0.1)
Testis	2 (0.0)	1 (0.0)	1 (0.1)
Vulva	2 (0.0)	2 (0.0)	0 (0.0)
More than one of the above diagnoses	1,950 (36.1)	1,698 (36.9)	252 (31.1)
None of the above diagnoses	313 (5.8)	237 (5.2)	76 (9.4)

[a]Studies with more than one cancer type are counted in the row "More than one of the above diagnoses" and excluded from the counts for the individual cancer types.

system cancers, which had the lowest estimated incidence among the five most-studied cancer diagnoses, also had the fewest available trial openings (n = 3,952).

In total, the available trial enrollment slots account for 8% of the estimated incident cases of cancer. Lung and bronchus cancers had the highest ratio of incident cases versus available enrollment slots (Table 3) among the most-studied cancer diagnoses, with 20 incident cases per trial opening. Table 3 lists a summary of all ratios by diagnosis. Across all cancer diagnoses, the Spearman correlation coefficient (95% confidence interval) for 2017 incident cases compared with projected 12-month enrollment were 0.79 (95% CI, 0.61 to 0.89) and 0.78 (95% CI, 0.59 to 0.89) compared with projected enrollment prorated for US sites, which shows a moderate correlation between incident cases and available trial enrollment slots across various cancer diagnoses.

DISCUSSION

Our estimate indicates that approximately 8% of patients (ie, 1 in every 13) would need to be enrolled to meet accrual demands. While this might suggest an excess of patients, not every patient can enroll in a clinical trial because of institutional, patient, or trial design barriers.[7] Therefore, some necessary minimum ratio of patients per trial opening (NMRPTO) would be needed to account for the system losses that these barriers cause. A recent meta-analysis

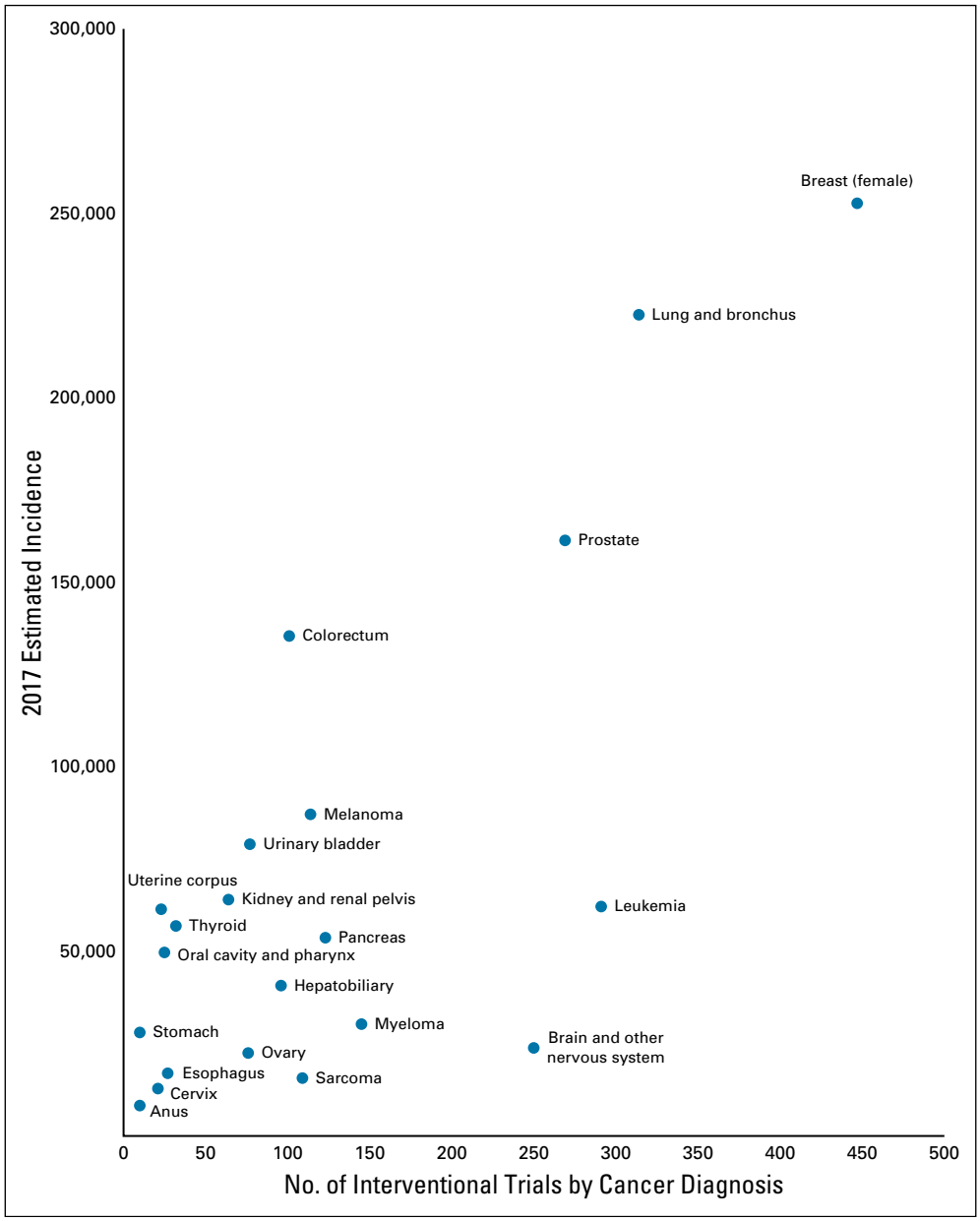

FIG 2. Comparison of 2017 estimated incidence of common cancer diagnoses versus number of interventional trials in the Database for Aggregate Analysis of ClinicalTrials.gov with US sites listed as actively recruiting at the beginning of September 2017.

demonstrated that across 13 institutions, the average ratio of patients with diagnoses matching open local trials to actual enrolled patients was 5.4.[12] The ratio at individual institutions was as high as 8.4, with variations likely attributable to the sites' trial portfolio and recruitment practices. Of note, these analyses are local and did not account for losses that were due to geographic barriers because the analysis was based only on trials at a given site. Accounting for geographic barriers would drive the system losses even higher, increasing the NMRPTO when calculated at a national level. In light of observed system losses, many of the specific disease ratios calculated here (eg, brain, 6.0; endocrine, 6.4; ovary, 9.3) approach the observed local NMRPTO of 5.4 and indicate that there may be insufficient patients to fill trials in these diseases without reducing losses through specific interventions like relaxing eligibility criteria, increasing trial locations, or screening more rigorously.

Having the minimum pool of patients globally available does not ensure sufficient accrual. Previous analysis of National Cancer Institute trials that failed to accrue found that such trials had to capture twice the proportion of potential trial participants as nonfailing trials and had more trials that competed for the same patients,[13] which reinforces the idea that successfully enrolling trials require not only the minimum

TABLE 2. Characteristics of Cancer Studies

Characteristic	Cancer Study Type, No. (%)		
	All (N = 5,407)	Interventional (n = 4,598)	Observational (n = 809)
Funding source			
Industry	2,093 (38.7)	1,977 (43.0)	116 (14.3)
National Institutes of Health	1,241 (23.0)	1,034 (22.5)	207 (25.6)
Other	2,073 (38.3)	1,587 (34.5)	486 (60.1)
Start year			
≤ 2011	570 (10.5)	321 (7.0)	249 (30.8)
2012	225 (4.2)	190 (4.1)	35 (4.3)
2013	387 (7.2)	318 (6.9)	69 (8.5)
2014	629 (11.6)	532 (11.6)	97 (12.0)
2015	1,103 (20.4)	978 (21.3)	125 (15.5)
2016	1,431 (26.5)	1,291 (28.1)	140 (17.3)
2017	1,062 (19.6)	968 (21.1)	94 (11.6)
Anticipated year for completion of follow-up for primary end point			
2017	768 (14.2)	639 (13.9)	129 (15.9)
2018	2,007 (37.1)	1,724 (37.5)	283 (35.0)
2019	1,216 (22.5)	1,089 (23.7)	127 (15.7)
2020	688 (12.7)	602 (13.1)	86 (10.6)
2021	296 (5.5)	260 (5.7)	36 (4.4)
≥ 2022	432 (8.0)	284 (6.2)	148 (18.3)
Total enrollment (anticipated)			
No.	5,407	4,598	809
Mean (SD)	311 (1,143)	167 (589)	1,129 (2,445)
Median (25th-75th)	70 (36-175)	60 (32-135)	229 (85-1,000)
Total duration[a] (anticipated), months			
No.	5,407	4598	809
Mean (SD)	62 (94)	50 (36)	132 (215)
Median (25th-75th)	43 (30-62)	41 (30-61)	61 (37-128)
Location of facilities			
United States only	4,543 (84.0)	3,792 (82.5)	751 (92.8)
Both United States and foreign	864 (16.0)	806 (17.5)	58 (7.2)
No. of arms/groups			
Single	2,992 (55.8)	2,417 (52.7)	575 (73.4)
> 1	2,373 (44.2)	2,165 (47.3)	208 (26.6)
For interventional studies			
Phase of trial			
≤ II		3,372 (73.3)	
II/III, III, IV		418 (9.1)	
NA		808 (17.6)	
Assignment to intervention arm			
NA: single study		2,357 (51.8)	
Randomized		1,277 (28.1)	
Nonrandomized		913 (20.1)	

(Continued on following page)

TABLE 2. Characteristics of Cancer Studies (Continued)

Characteristic	Cancer Study Type, No. (%)		
	All (N = 5,407)	Interventional (n = 4,598)	Observational (n = 809)
Intervention type[b]			
Behavioral		318 (6.9)	
Biologic		730 (15.9)	
Combination		7 (0.2)	
Device		256 (5.6)	
Diagnostic test		21 (0.5)	
Dietary supplement		41 (0.9)	
Drug		3,325 (72.3)	
Genetic		41 (0.9)	
Radiation		592 (12.9)	
Other intervention		952 (20.7)	

Abbreviations: NA, not applicable; SD, standard deviation.

[a]Duration defined as the number of months from study start to completion of follow-up for the primary end point(s).

[b]A study may have more than one intervention type and be counted in multiple rows.

pool of patients from which to enroll but also larger pools of patients in excess of the NMRPTO to increase the odds of recruitment success. This analysis evaluates the ratios of unscreened patients with cancer available for each clinical trial opening both across cancer types and by cancer diagnosis. These ratios are intended to shed light on the relative difficulty of patient accrual on the basis of the global supply and demand of trial openings and unscreened patients.

Among cancers with the highest estimated incidence, trials that treat cancers of the lung, colorectum, urinary bladder, and melanoma of the skin seem to have a greater likelihood of meeting accrual goals because they each have at least 20 incident cases for each opening. For cancers of the brain and nervous system, one of the most studied cancer diagnoses, there are only 6 incident cases per potential trial enrollment slot. These trials are likely to face greater challenges in meeting trial demands when other barriers like patient eligibility and local availability of trials are considered. Other cancer diagnoses have a remarkably large number of incident cases per trial opening relative to the rest. This may be due to the limited number of active trials and reflects the issue of year-specific variations in trial activation such that within certain years, only a few active trials may be available for certain cancer diagnoses. However, it may also indicate a limitation in our study methodology because trials with more than one diagnosis were excluded from analyses of individual diagnoses. This may result in a lower estimate of available trial enrollment slots for particular diagnoses, which predominantly had trials that included more than one cancer diagnosis.

These findings may impact rates of accrual failure among trials in the US clinical trial portfolio in several ways. For trials that appear to have a sufficient patient population, it reinforces the importance of current efforts to reduce barriers to enrollment that are being conducted across all levels of the clinical trial enterprise. Trial availability varies widely depending on the type of institution, with large academic centers offering more trial options than community or physician-based practices, and, indeed, lack of trial availability. Ultimately, for cancers where trials continue to fall short of meeting enrollment goals despite the assumption that an adequate number of patients is available, the focus should be on improved patient access to existing trials.[14]

Cancer diagnoses that have a relatively low ratio of incident cases to trial openings may have difficulty with meeting enrollment goals because of expected losses as a result of barriers and competition for a very limited patient pool. In this case, it may be necessary to either condense the number of trials or expand eligibility criteria to maximize the quantity of potential patients. However, if the incidence of any particular cancer diagnosis is too low relative to trial openings, trials with impractical expectations for accrual may be doomed to fail at inception regardless of any efforts to expand eligibility.[15]

While we acknowledge that this is a broad, macroscopic analysis of the available patient population for oncology trials, it can nevertheless guide discussion and serve as evidence that there may not be a one-size-fits-all solution when it comes to addressing the issue of inadequate trial participation. There appears to be a minimum number of patients with cancer in the United States to meet accrual demands of domestic oncology clinical trials. Enrollment opportunities exist for 1 (8%) in every 13 of the diagnosed population of patients with cancer at full steady-state accrual, which indicates the imputed capacity of the existing trial portfolio. Enrollment rates $< 8\%$ would cause existing trials to accrue more slowly than planned or for some trials

TABLE 3. Estimated 2017 Incidence and Mortality by Cancer Diagnosis and Projected 12-Month Enrollment of US Interventional Studies

Cancer Diagnosis[a,b]	2017 New Cases, No.	2017 New Deaths, No.	Total, Prorated for US Sites			Estimated Incident Cancers for Each Enrollment Slot, No.
			Studies, No.	Enrollment Slots, No.	Cases, %	
All sites	1,688,780	600,920	4,598	134,339	8.0	12.6
Breast (female)	252,710	40,610	447	18,294	7.2	13.8
Lung and bronchus	222,500	155,870	314	11,077	5.0	20.1
Prostate	161,360	26,730	269	9,163	5.7	17.6
Colorectum	135,430	50,260	101	5,484	4.0	24.7
Melanoma of the skin	87,110	9,730	114	3,639	4.2	23.9
Urinary bladder	79,030	16,870	77	2,675	3.4	29.5
Non-Hodgkin lymphoma	72,240	20,140	5	55	0.1	1,313.5
Kidney and renal pelvis	63,990	14,400	64	1,863	2.9	34.3
Leukemia	62,130	24,500	291	5,366	8.6	11.6
Uterine corpus	61,380	10,920	23	1,037	1.7	59.2
Thyroid	56,870	2,010	32	532	0.9	106.9
Pancreas	53,670	43,090	123	2,407	4.5	22.3
Oral cavity and pharynx	49,670	9,700	25	547	1.1	90.8
Hepatobiliary	40,710	28,920	96	1,665	4.1	24.5
Myeloma	30,280	12,590	145	2,571	8.5	11.8
Stomach	28,000	10,960	10	241	0.9	116.2
Brain and other nervous system	23,800	16,700	250	3,952	16.6	6.0
Ovary	22,440	14,080	76	2,418	10.8	9.3
Esophagus	16,940	15,690	27	516	3.0	32.8
Sarcoma	15,650	6,540	109	1,606	10.3	9.7
Larynx	13,360	3,660	4	27	0.2	494.8
Uterine cervix	12,820	4,210	21	943	7.4	13.6
Testis	8,850	410	1	11	0.1	804.5
Hodgkin lymphoma	8,260	1,070	2	80	1.0	103.3
Anus	8,200	1,100	10	778	9.5	10.5
Vulva	6,020	1,150	2	22	0.4	273.6
Eye	3,130	330	5	126	4.0	24.8
Other endocrine	2,380	1,000	20	371	15.6	6.4

[a]For enrollment by cancer diagnosis, studies with more than one cancer diagnosis are excluded from the counts for the individual diagnoses. The 2017 estimated counts of incidence (new cases) and mortality (new deaths) are for the United States. Except for breast cancer, counts are combined for females and males. For breast cancer, counts are for females. For colorectum cancer studies, incidence and mortality are for colon and rectum. For hepatobiliary cancer studies, incidence and mortality are for liver and intrahepatic bile duct. For sarcoma cancer studies, incidence and mortality are for bones, joints, and soft tissue (including the heart). For anus cancer studies, incidence and mortality are for anus, anal canal, and anorectum. For eye cancer studies, incidence and mortality are for eye and orbit.

[b]Estimates of incidence are model-based, 4-year-ahead projections and, thus, also have limitations in and of themselves. This may result in over- or underestimation of occurrence of each cancer type.

to even fail because of low accrual, which is the current case. Enrollment rates > 8% would result in trials that reach accrual goals faster than anticipated or indicate a capacity for the system to expand to more accruing trials. However, it is clear that the degree of concordance between demand of trial openings and supply of available patients varies for each cancer diagnosis.

Several limitations of the current study exist. More than one third (37%) of the interventional oncology trials identified using our methods were classified under more than one cancer diagnosis and were excluded from our analysis of trial openings for individual diagnoses. Thus, the ability to interpret the ratio of estimated incident cases to each available trial opening as a marker of trial enrollment feasibility is limited for some cancer types because of potential undercounting of enrollment. Our estimate of available trial enrollment slots that account for 8% of the incident cases of cancer is likely an under-representation of the true value

because this is based on only approximately 60% of the interventional trials. The majority of the cancer diagnoses are represented in > 40% of the trials that were not disease specific (Appendix Table A4), which hinders our ability to apportion available enrollment slots from these trials to individual diagnoses. However, the primary objective of this study was to provide a broad overview of available trial enrollment slots for all cancer diagnoses combined, which is unaffected by this limitation. A more granular review of these trials in the future would enhance the accuracy of the estimates and allow for a greater understanding of enrollment feasibility of each cancer type.

Our study was also limited by the information captured by the AACT, with challenges related to missing data, a lack of a standardized terminology system when entering these trials into the database, and lack of accrual information.[16] These data would better describe accrual patterns and improve trial design. Using the date at which follow-up of the primary end point was completed as a surrogate for enrollment completion date could result in overestimation of the duration of patient enrollment or underestimation of the average annual accrual rate for studies, particularly if this date is much later than the actual enrollment completion date. Furthermore, the trials that were excluded because of missing information may be systematically different from those included in our analysis. We were unable to correlate trial availability by geography. We were unable to adjust for variations in eligibility, such as genomic targets. Of note, enrollment in a trial is not determined solely by availability of a slot. We were unable to fully distinguish between pediatric and adult trials; however, only 1.4% of interventional trials were restricted to pediatric patients, which represents a small proportion. Numerous other factors also play a role, including physician workflow, staff availability, travel, cost, and inherent biases against trial participation, among others. These limitations of the AACT make it difficult to accurately describe the clinical trial portfolio and perform a more complex analysis.

In conclusion, the issues of slow accrual and early termination of trials before reaching full accrual tax already-limited resources of the research enterprise. With ever-increasing demands for a seemingly narrowing pool of eligible patients, it is important to investigate whether the failure of clinical trials to meet enrollment goals is due to an actual shortage of patients or other factors. Our findings may guide trialists and policymakers to bolster resources where incidence may be too low to support the current number of trials. In these settings, opening trials at more locations, designing pragmatic trials, and limiting exclusion criteria may improve participation rates.

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APPENDIX

TABLE A1. Excluded Studies With > 20,000 Estimated Enrollment

ClinicalTrials.gov Identifier	Brief Title	Study Type	Estimated Enrollment
NCT01239082	Colonoscopy Versus Fecal Immunochemical Test in Reducing Mortality From Colorectal Cancer (CONFIRM)	Interventional	50,000
NCT02620852	Women Informed to Screen Depending on Measures of Risk	Interventional	100,000
NCT03058926	Coordinating and Data Management Center for the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer	Observational	25,000
NCT02402244	Project: Every Child for Younger Patients With Cancer	Observational	33,000
NCT01120353	Childhood Cancer Survivor Study	Observational	50,000
NCT03008980	The Analysis of WATS3D (Wide Area Transepithelial Sample Biopsy With 3-Dimensional Computer-Assisted Analysis) Increased Yield of Barrett's Esophagus and Esophageal Dysplasia	Observational	75,000
NCT01351545	A Multicenter Access and Distribution Protocol for Unlicensed Cryopreserved Cord Blood Units (CBUs)	Observational	99,999
NCT02695121	Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment	Observational	99,999
NCT02334085	The Health of Women Study	Observational	100,000
NCT03061305	Profiling Biospecimens From Cancer Patients to Screen for Molecular Alterations Related to Treatment Selection	Observational	100,000
NCT01166009	Protocol for a Research Database for Hematopoietic Stem Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries	Observational	99,999,999

TABLE A2. Characteristics of Interventional Cancer Studies for the Most Frequently Studied Cancer Diagnoses

Characteristic	Cancer Study Type, No. (%)					
	All (n = 4,598)	Breast (female) (n = 447)	Brain and Other Nervous System (n = 250)	Leukemia (n = 291)	Lung and Bronchus (n = 314)	Prostate (n = 269)
Funding source						
Industry	1,977 (43.0)	143 (32.0)	73 (29.2)	154 (52.9)	160 (51.0)	81 (30.1)
National Institutes of Health	1,034 (22.5)	100 (22.4)	52 (20.8)	50 (17.2)	73 (23.2)	60 (22.3)
Other	1,587 (34.5)	204 (45.6)	125 (50.0)	87 (29.9)	81 (25.8)	128 (47.6)
Start year						
≤ 2011	321 (7.0)	19 (4.3)	25 (10.0)	18 (6.2)	17 (5.4)	25 (9.3)
2012	190 (4.1)	15 (3.4)	16 (6.4)	15 (5.2)	12 (3.8)	8 (3.0)
2013	318 (6.9)	35 (7.8)	18 (7.2)	23 (7.9)	18 (5.7)	11 (4.1)
2014	532 (11.6)	47 (10.5)	29 (11.6)	38 (13.1)	28 (8.9)	36 (13.4)
2015	978 (21.3)	108 (24.2)	40 (16.0)	69 (23.7)	85 (27.1)	58 (21.6)
2016	1,291 (28.1)	133 (29.8)	72 (28.8)	83 (28.5)	85 (27.1)	71 (26.4)
2017	968 (21.1)	90 (20.1)	50 (20.0)	45 (15.5)	69 (22.0)	60 (22.3)
Anticipated year for completion of follow-up for primary end point						
2017	639 (13.9)	58 (13.0)	41 (16.4)	40 (13.7)	43 (13.7)	34 (12.6)
2018	1,724 (37.5)	178 (39.8)	86 (34.4)	91 (31.3)	114 (36.3)	104 (38.7)
2019	1,089 (23.7)	108 (24.2)	59 (23.6)	76 (26.1)	78 (24.8)	53 (19.7)
2020	602 (13.1)	54 (12.1)	32 (12.8)	39 (13.4)	48 (15.3)	44 (16.4)
2021	260 (5.7)	19 (4.3)	19 (7.6)	20 (6.9)	14 (4.5)	20 (7.4)
≥ 2022	284 (6.2)	30 (6.7)	13 (5.2)	25 (8.6)	17 (5.4)	14 (5.2)
Total enrollment (anticipated)						
No.	4,598	447	250	291	314	269
Mean (SD)	167 (589)	238 (576)	81 (107)	101 (112)	209 (633)	185 (335)
Median (25th-75th)	60 (32-135)	76 (37-180)	43 (24-87)	60 (39-119)	66 (36-170)	70 (36-165)
Total duration[a] (anticipated), months						
No.	4,598	447	250	291	314	269
Mean (SD)	50 (36)	47 (28)	52 (33)	56 (63)	47 (29)	51 (33)
Median (25th-75th)	41 (30-61)	39 (26-59)	44 (29-62)	48 (34-64)	39 (29-54)	43 (32-61)
Locations of facilities						
United States only	3,792 (82.5)	385 (86.1)	226 (90.4)	241 (82.8)	244 (77.7)	236 (87.7)
Both United States and foreign	806 (17.5)	62 (13.9)	24 (9.6)	50 (17.2)	70 (22.3)	33 (12.3)
No. of arms/groups						
Single	2,417 (52.7)	215 (48.5)	154 (61.8)	153 (52.9)	155 (49.5)	127 (47.4)
> 1	2,165 (47.3)	228 (51.5)	95 (38.2)	136 (47.1)	158 (50.5)	141 (52.6)
For interventional studies						
Phase of trial						
≤ II	3,372 (73.3)	260 (58.2)	183 (73.2)	250 (85.9)	222 (70.7)	163 (60.6)
II/III, III, IV	418 (9.1)	43 (9.6)	17 (6.8)	31 (10.7)	47 (15.0)	39 (14.5)
NA	808 (17.6)	144 (32.2)	50 (20.0)	10 (3.4)	45 (14.3)	67 (24.9)
Assignment to intervention arm						
NA: single study	2,357 (51.8)	212 (48.0)	151 (60.9)	150 (52.1)	152 (49.2)	124 (46.6)
Randomized	1,277 (28.1)	180 (40.7)	51 (20.6)	66 (22.9)	105 (34.0)	105 (39.5)
Nonrandomized	913 (20.1)	50 (11.3)	46 (18.5)	72 (25.0)	52 (16.8)	37 (13.9)

(Continued on following page)

TABLE A2. Characteristics of Interventional Cancer Studies for the Most Frequently Studied Cancer Diagnoses (Continued)

Characteristic	Cancer Study Type, No. (%)					
	All (n = 4,598)	Breast (female) (n = 447)	Brain and Other Nervous System (n = 250)	Leukemia (n = 291)	Lung and Bronchus (n = 314)	Prostate (n = 269)
Intervention type[b]						
Behavioral	318 (6.9)	63 (14.1)	8 (3.2)	9 (3.1)	13 (4.1)	29 (10.8)
Biologic	730 (15.9)	33 (7.4)	42 (16.8)	38 (13.1)	47 (15.0)	29 (10.8)
Combination	7 (0.2)	2 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Device	256 (5.6)	35 (7.8)	32 (12.8)	2 (0.7)	12 (3.8)	20 (7.4)
Diagnostic test	21 (0.5)	2 (0.4)	2 (0.8)	1 (0.3)	1 (0.3)	3 (1.1)
Dietary supplement	41 (0.9)	5 (1.1)	1 (0.4)	0 (0.0)	2 (0.6)	2 (0.7)
Drug	3,325 (72.3)	269 (60.2)	171 (68.4)	268 (92.1)	231 (73.6)	169 (62.8)
Genetic	41 (0.9)	3 (0.7)	3 (1.2)	3 (1.0)	4 (1.3)	1 (0.4)
Radiation	592 (12.9)	41 (9.2)	61 (24.4)	9 (3.1)	66 (21.0)	56 (20.8)
Other intervention	952 (20.7)	98 (21.9)	39 (15.6)	48 (16.5)	72 (22.9)	61 (22.7)

NOTE. Studies that occur in more than one cancer type have been excluded from the specific cancer type columns.
Abbreviations: NA, not applicable; SD, standard deviation.
[a]Duration defined as the number of months from study start to completion of follow-up for the primary endpoint(s).
[b]A study may have more than one intervention type and be counted in multiple rows.

TABLE A3. Characteristics of Observational Cancer Studies for the Most Frequently Studied Cancer Diagnoses

Characteristic	Cancer Study Type, No. (%)					
	All (n = 809)	Breast (female) (n = 96)	Brain and Other Nervous System (n = 45)	Leukemia (n = 31)	Lung and Bronchus (n = 53)	Prostate (n = 59)
Funding source						
Industry	116 (14.3)	13 (13.5)	4 (8.9)	7 (22.6)	15 (28.3)	14 (23.7)
National Institutes of Health	207 (25.6)	23 (24.0)	12 (26.7)	3 (9.7)	14 (26.4)	14 (23.7)
Other	486 (60.1)	60 (62.5)	29 (64.4)	21 (67.7)	24 (45.3)	31 (52.5)
Start year						
≤ 2011	249 (30.8)	28 (29.2)	13 (28.9)	7 (22.6)	15 (28.3)	11 (18.6)
2012	35 (4.3)	2 (2.1)	1 (2.2)	1 (3.2)	7 (13.2)	1 (1.7)
2013	69 (8.5)	11 (11.5)	4 (8.9)	5 (16.1)	3 (5.7)	7 (11.9)
2014	97 (12.0)	12 (12.5)	5 (11.1)	0 (0.0)	9 (17.0)	9 (15.3)
2015	125 (15.5)	14 (14.6)	9 (20.0)	8 (25.8)	10 (18.9)	11 (18.6)
2016	140 (17.3)	14 (14.6)	8 (17.8)	6 (19.4)	7 (13.2)	12 (20.3)
2017	94 (11.6)	15 (15.6)	5 (11.1)	4 (12.9)	2 (3.8)	8 (13.6)
Anticipated year for completion of follow-up for primary end point						
2017	129 (15.9)	20 (20.8)	7 (15.6)	4 (12.9)	14 (26.4)	8 (13.6)
2018	283 (35.0)	35 (36.5)	16 (35.6)	12 (38.7)	19 (35.8)	23 (39.0)
2019	127 (15.7)	18 (18.8)	8 (17.8)	5 (16.1)	8 (15.1)	13 (22.0)
2020	86 (10.6)	10 (10.4)	6 (13.3)	4 (12.9)	1 (1.9)	8 (13.6)
2021	36 (4.4)	3 (3.1)	2 (4.4)	1 (3.2)	2 (3.8)	1 (1.7)
≥ 2022	148 (18.3)	10 (10.4)	6 (13.3)	5 (16.1)	9 (17.0)	6 (10.2)
Total enrollment (anticipated)						
No.	809	96	45	31	53	59
Mean (SD)	1,129 (2,445)	608 (1,245)	546 (1,582)	757 (1,779)	1,057 (2,138)	817 (1,618)
Median (25th-75th)	229 (85-1,000)	164 (65-700)	105 (82-320)	300 (50-1,000)	250 (100-1,000)	200 (60-600)
Total duration[a] (anticipated), months						
No.	809	96	45	31	53	59
Mean (SD)	132 (215)	116 (207)	119 (199)	109 (191)	132 (218)	72 (62)
Median (25th-75th)	61 (37-128)	54 (31-121)	58 (37-116)	59 (37-123)	61 (38-121)	57 (30-97)
Locations of facilities						
United States only	751 (92.8)	93 (96.9)	40 (88.9)	29 (93.5)	52 (98.1)	56 (94.9)
Both United States and foreign	58 (7.2)	3 (3.1)	5 (11.1)	2 (6.5)	1 (1.9)	3 (5.1)
No. of arms/groups						
Single	575 (73.4)	70 (72.9)	35 (79.5)	23 (76.7)	39 (75.0)	45 (78.9)
> 1	208 (26.6)	26 (27.1)	9 (20.5)	7 (23.3)	13 (25.0)	12 (21.1)

NOTE. Studies that occur in more than one cancer type have been excluded from the specific cancer type columns.
Abbreviation: SD, standard deviation.
[a]Duration defined as the number of months from study start to completion of follow-up for the primary endpoint(s).

TABLE A4. Frequency of Cancer Diagnoses in Trials With More Than One Diagnosis

Cancer Diagnosis[a]	Cancer Study Type, No. (%)		
	All Multicancer (N= 1,950)	Interventional (n = 1,698)	Observational (n = 252)
Breast (female)	969 (49.7)	831 (48.9)	138 (54.8)
Prostate	887 (45.5)	763 (44.9)	124 (49.2)
Lung and bronchus	965 (49.5)	824 (48.5)	141 (56.0)
Colorectum	924 (47.4)	790 (46.5)	134 (53.2)
Uterine corpus	898 (46.1)	774 (45.6)	124 (49.2)
Urinary bladder	890 (45.6)	770 (45.3)	120 (47.6)
Melanoma of the skin	790 (40.5)	663 (39.0)	127 (50.4)
Non-Hodgkin lymphoma	1,151 (59.0)	1,020 (60.1)	131 (52.0)
Kidney and renal pelvis	895 (45.9)	771 (45.4)	124 (49.2)
Thyroid	852 (43.7)	735 (43.3)	117 (46.4)
Leukemia	963 (49.4)	834 (49.1)	129 (51.2)
Pancreas	935 (47.9)	797 (46.9)	138 (54.8)
Ovary	928 (47.6)	794 (46.8)	134 (53.2)
Oral cavity and pharynx	1,019 (52.3)	885 (52.1)	134 (53.2)
Uterine cervix	886 (45.4)	763 (44.9)	123 (48.8)
Hepatobiliary	884 (45.3)	760 (44.8)	124 (49.2)
Stomach	898 (46.1)	767 (45.2)	131 (52.0)
Brain and other nervous system	923 (47.3)	800 (47.1)	123 (48.8)
Myeloma	762 (39.1)	652 (38.4)	110 (43.7)
Testis	859 (44.1)	738 (43.5)	121 (48.0)
Esophagus	888 (45.5)	764 (45.0)	124 (49.2)
Larynx	1,011 (51.8)	879 (51.8)	132 (52.4)
Hodgkin lymphoma	1,151 (59.0)	1,006 (59.2)	145 (57.5)
Sarcoma	923 (47.3)	793 (46.7)	130 (51.6)
Other endocrine	33 (1.7)	20 (1.2)	13 (5.2)
Small intestine	3 (0.2)	0 (0.0)	3 (1.2)
Anus	10 (0.5)	5 (0.3)	5 (2.0)
Eye	27 (1.4)	21 (1.2)	6 (2.4)
Vagina	9 (0.5)	6 (0.4)	3 (1.2)
Vulva	10 (0.5)	7 (0.4)	3 (1.2)
Penis	3 (0.2)	2 (0.1)	1 (0.4)

[a]Studies in this table were assigned to more than one type of cancer, and a single study may be counted in multiple rows of the table.