Survey of public information about ongoing clinical trials funded by industry: evaluation of completeness and accessibility

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Abstract

Objective To evaluate the completeness and accessibility of public information about US clinical trials of drugs in development.

Design Review of online registers of clinical trials.

Data sources Drugs in phase III trials were identified using three drug industry sources: PhRMA Survey, What's in the Pipeline, and the NDA Pipeline. Drug trials were then searched for on the following publicly accessible registers of clinical trials: CancerNet.gov, CenterWatch.com, ClinicalTrials.gov, and registers associated with the 37 "Comprehensive Cancer Centers" designated by the National Cancer Institute.

Main outcome measure Extent of availability of public information on phase III trials of drugs in development for treating either prostate or colon cancer.

Results Search of industry sources identified 12 drugs for prostate cancer and 20 for colon cancer undergoing phase III trials. The most comprehensive publicly available register, ClinicalTrials.gov, contained trial listings for only seven of the prostate cancer drugs and 10 of the colon cancer drugs. Trials of three prostate cancer and three colon cancer drugs were listed on only one register each. A substantial proportion of trials of prostate cancer drugs (3/12) and colon cancer drugs (8/20) were not associated with trial listings in any registers.

Conclusions Existing trials registers are unlikely to be meeting user needs since many ongoing drug trials are not listed. There is a clear need for a comprehensive clinical trials register encompassing all ongoing trials, including industry sponsored trials.

Introduction

No comprehensive system for tracking, organising, and disseminating information about ongoing clinical trials currently exists. Selected trials are instead registered in one or more of hundreds of distinct, predominantly online registers.[1] The absence of a comprehensive, standardised register creates problems for clinicians[2] and patients[3] seeking information about ongoing trials and for reviewers preparing and maintaining systematic reviews. Because reviewers cannot easily identify all trials started on a given drug, reviews are often limited to published trials; if the published trials are not representative of all trials undertaken, the systematic review may be unreliable.[4–6] Clinicians who make treatment decisions based on biased systematic reviews or treat without the benefit of any trial evidence risk doing more harm than good.

We undertook a study to see whether information about trials of experimental drugs for prostate and colon cancer was available using online, US based trials registers.

Methods

We limited our evaluation to US based, phase III or phase II-III trials of drugs in development (hereafter referred to as phase III trials) for the treatment of either prostate cancer or colon cancer, the two cancers most heavily investigated by pharmaceutical companies.[7] Phase III trials test drugs that have already shown safety and some efficacy in phase I and II trials respectively and are the final phase of testing new drugs before approval for use in patients. Phase III trials generally compare an experimental treatment with the current standard treatment or a placebo, involve relatively large numbers of participants, and, according to an Eli Lilly website statement from October 1999, include 90% of all patients and volunteers involved in drug testing.

Data sources

We selected two distinct types of data sources: firstly, industry data sources about drugs in development ("pipeline sources") and, secondly, publicly available sources of information about ongoing trials of these drugs ("online trials registers"). Two of our three pipeline sources, NDA Pipeline and PhRMA 1999 Survey, report on US drug development and are described respectively as providing "a complete picture of US drug research activities"[8] and listing pipeline drugs for "100 US companies that have a primary commitment to pharmaceutical research."[9] Our third pipeline source, What's in the Pipeline, June 1999 and June 2000, provides multinational coverage, and the country of development is included for each drug listing.[10 11]

Pipeline sources

We conducted a comprehensive search of each pipeline source to identify US developed drugs for

P+ *An extra table listing alternative names for drugs appears on bmj.com*

treating either prostate cancer or colon cancer. For practical reasons, our study was completed in two phases: the prostate cancer phase was completed in March-April 2000 and the colon cancer phase in October-November 2000. For both the prostate cancer and colon cancer drug searches we used the PhRMA 1999 Survey and the NDA Pipeline (as of January 2000) as these were the most up to date sources available to us through November 2000. We searched the 1999 version of What's in the Pipeline for prostate cancer drugs and the 2000 version for colon cancer drugs.

Information was not standardised across the three data sources. For example, some drugs were identified by their chemical name in one pipeline source and by their generic or trade name in another. We found different spellings of the same drug name across pipeline sources. In addition, there were cases where we were not certain whether two different names referred to two different drugs or were synonyms for the same drug; for example, Abarelix and PPI-149 were listed as two distinct products in What's in the Pipeline and as alternative names for the same product in the NDA Pipeline. To eliminate duplicate listings of the same drug and to insure that we had all available synonyms and correct spellings for each identified drug, we also checked the websites of the companies that developed the drugs on our list and catalogued any additional drug names identified.

Online trials registers

To ascertain the availability of information about trials testing these experimental drugs on US based online trials registers, we searched the following online trials registers: CancerNet.gov (now named Cancer.gov), CenterWatch.com, ClinicalTrials.gov, and the trials registers for the 37 "Comprehensive Cancer Centers" designated by the National Cancer Institute. We searched these online trials registers in April 2000 for prostate cancer trials and in November 2000 for colon cancer trials. We searched the registers using either a visual scan for trials listed under the headings "prostate cancer" or "colon cancer," each register's search dialogue box, or the browser's "find in page" function. We used all possible synonyms of a drug name to search for each drug. For drugs not found on any trials register, we attempted to confirm that a US phase III trial was conducted by directly contacting the drug developer.

Results

Pipeline sources

We identified 12 drugs under development for prostate cancer and 20 drugs under development for colon cancer. As many as five different names were used to describe the same drug (see table A on bmj.com). Few of the drugs for prostate cancer (2/12) or colon cancer (1/20) were listed in all pipeline sources, and about half were listed in only one source (5/12 prostate cancer drugs, 12/20 colon cancer drugs) (see table 1). We only had information on drugs that were listed in at least one of the pipeline sources we searched; there may be other drugs in phase III trials that were not listed in any of our pipeline sources.

Table 1 Number of drug industry "pipeline" sources (NDA Pipeline, PhRMA 1999 Survey, and What's in the Pipeline June 1999 and June 2000) listing drugs for prostate cancer and colon cancer in phase III trials

	Pipeline source		
Drug	**NDA Pipeline**	**PhRMA**	**What's in the Pipeline**
Prostate cancer drugs			
RL-0903	√	√	√
Exisuland	√	√	√
Leuprolide acetate	√	√	
ALRT-1057	√	√	
PPI-149	√		√
Bicalutimide	√		√
Duros leuprolide		√	√
AG3340		√	√
SU101		√	
BMS-217380		√	
Goserelin acetate			√
Aredia			√
Colon cancer drugs			
multitargeted antifolate	√	√	√
CPT-11	√	√	
SU-5416	√		√
eniluracil	√		√
edrecolomab	√		√
trimetrexate glucuronate		√	√
CeaVac		√	√
capecitabine		√	√
eflornithine	√		
recombinant interferon-beta-1a		√	
OncoVAXcl		√	
neutralize hormone G17		√	
Mab 17-1A		√	
Exisuland		√	
Eloxatin		√	
VEGF			√
Raltitrexed			√
Octreotide acetate			√
Avicine			√
Anti-Gastrin			√

Online trials registers

None of the online trials registers listed trials for all of the 12 prostate cancer drugs or all of the 20 colon cancer drugs we identified. For three each of the prostate cancer and colon cancer drugs, associated trials were listed on only one register. Few drugs (one for prostate cancer and three for colon cancer) had associated trials listed on all of the online registers (table 2). ClinicalTrials.gov was the most comprehensive of the registers, but even this listed trials for only seven of the prostate cancer drugs and 10 of the colon cancer drugs.

A relatively large proportion of the pipeline drugs (3/12 prostate cancer drugs and 8/20 colon cancer drugs) did not appear in any of the online registers searched. We confirmed that phase III US trials were conducted for two of these prostate cancer drugs and five of the colon cancer drugs not listed on any register. For the rest, the company contact either explicitly stated that no phase III trial had yet been conducted anywhere (one prostate cancer drug and one colon cancer drug) or the contact could not locate any information about any US based phase III trial of the drug (two colon cancer drugs). In no case were we told that a phase III trial had been conducted but was performed outside the US.

Table 2 Number of US based online trials registers listing phase III trials of drugs for prostate cancer and colon cancer identified from pipeline sources

	Online register			
Drug	**CancerNet.gov**	**Comprehensive Cancer Centers**	**CenterWatch.com**	**ClinicalTrials.gov**
Prostate cancer drugs				
AG3340	√	√	√	√
Leuprolide acetate	√	√		√
Goserelin acetate	√	√		√
Bicalutimide	√	√		√
SU101	√			√
Aredia			√	√
ALRT-1057				√
Exisuland		√		
PPI-149		√		
Duros leuprolide*				
RL-0903*				
BMS-217380†				
Colon cancer drugs				
Octreotide acetate	√	√	√	√
Mab 17-1A	√	√	√	√
Eloxatin	√	√	√	√
SU-5416	√	√		√
CPT-11	√	√		√
eflornithine	√			√
edrecolomab	√			√
VEGF		√		√
Raltitrexed		√		√
eniluracil		√		
multitargeted antifolate		√		
trimetrexate glucuronate				√
Avicine*				
capecitabine*				
CeaVac*				
Exisuland*				
neutralize hormone G17*				
OncoVAXcl†				
Anti-Gastrin‡				
recombinant interferon-beta-1a‡				

*Drug company confirmed that phase III US trials conducted.
†Drug company stated that no phase III trial conducted.
‡Drug company had no information about any US based phase III trial.

Discussion

No single pipeline information source listed all the drugs in phase III trials in our sample. In addition, the various pipeline sources often contained non-standardised and incomplete information, making it difficult to search for and summarise data about drugs in development. No one register, nor the sum of all included registers, listed every ongoing trial, with many trials identified in the pipeline sources not being listed in any of the registers. Pipeline source information sometimes contradicted information obtained from companies directly.

Searching several online registers to identify trials was cumbersome and time consuming, because of limitations in the organisation and search capacities of the websites and lack of standardisation and clarity of the language used to describe the trials. Some of the websites provided simply text lists of trial names; they lacked search engines and provided no groupings of trials by health condition. As a result, identifying trials required reading through all of the trials listed, or using the browser's "find in page" function to locate specific key words such as a drug name. Even if keyword searches could be performed quickly, they were not always reliable because of lack of standardisation of drug names and health conditions. Indexing trial listings using a thesaurus tree and a controlled vocabulary system such as Medline's Medical Subject Headings (MeSH) would theoretically ensure retrieval of the same set of trial listings, regardless of the "key words" used by searchers (for example, "prostate cancer" would map to MeSH "prostatic neoplasms").[12]

The lack of standardisation—coupled with the frequent absence of information such as drug name, phase of testing, and condition treated—contributed to the difficulty of using the websites. Thus, the same trial listed on several registers varied in the amount of information available. A unique identifier numbering system would have helped confirm that similar listings referred to the same trial.[13]

Various efforts have been made by independent groups to address the problem, but none is completely satisfactory. We have developed an interim online resource to help improve access to information about ongoing clinical trials, called TrialsCentral (www.trialscentral.org),[1] which links to hundreds of registers of ongoing US based trials. An international resource, Current Controlled Trials (www.controlled-trials.com), contains both a "register of registers" of controlled trials as well as a "metaregister of controlled trials," a searchable database of information on thousands of ongoing and completed randomised controlled trials. The metaregister is perhaps the best effort so far, but it is still far from comprehensive. The Cochrane Collaboration[14] has developed a database of published clinical trials available through the *Cochrane Library*.[15]

With the increasing recognition of the importance of registering ongoing trials,[16–18] several government supported initiatives have begun. For example, all trials funded by the UK NHS must be registered.[19] In the United States the Food and Drug Administration Modernization Act 1997, section 113, requires prospective registration of all clinical trials of efficacy conducted in the United States for serious or life

What is already known on this topic

There are hundreds of distinct, predominantly online registers of ongoing drug trials, with overlapping, non-standardised contents

The lack of organisation and centralisation of information on clinical trials poses problems for those seeking information about ongoing trials and for researchers preparing and maintaining systematic reviews

What this study adds

Pharmaceutical industry "pipeline sources" can be used as sources of information about drugs in clinical trial testing, but these sources often contain non-standardised and incomplete information, making it difficult to search for and summarise current testing activities

Many drugs that were identified as undergoing testing in pipeline sources were not listed in any of the trials registers searched

threatening conditions.[20] In response to this act, the US National Institutes of Health has created its largest clinical trials database, ClinicalTrials.gov.[21] However, even this database did not include trial listings for almost half of the 32 phase III drugs in our sample. Drug companies may not be willing to register their trials if registration is believed to compromise their commercial interests.

There is a pressing need for a transparent, comprehensive, and mandatory registration system for clinical trials. The best current sources of trial data are the institutional review boards or ethics committees, which theoretically have access to information on all initiated trials, at least in countries with such systems. Mandatory registration is the only sure route for obtaining information about ongoing and completed clinical trials funded by industry.[22] Making this information available is critical to protecting the rights of human volunteers who contribute their lives to health research efforts, and critical to moving biomedical research forward at maximum speed.

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Contributors: EM helped conceive and design the study, conducted the searches and extracted relevant data, contacted drug companies, analysed and interpreted the data, and drafted and revised the paper. DA helped conceive and design the study, provided resources and references, and contributed to revisions to the paper. EM is guarantor for the paper.

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