

Evaluating the Impact of *Clinical Trials On-Line* On Clinical Trial Awareness and Accrual

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Abstract

Clinical trials are essential for understanding the effects of different cancer treatment approaches and the value of their interaction. A prerequisite for completion of a clinical trial is the accrual of an adequate number of patients. Although surveys of the general public have shown widespread support for the concept of clinical trials, it is widely reported that only 1-3% of the 1.2 million patients diagnosed with cancer in the United States each year are enrolled. Explaining clinical trials to patients and their families, remembering active trials for a particular malignancy, and paper-based distribution of clinical trial information have been identified among several major obstacles to enrollment. Improved information distribution methods, heightened public awareness, and the dissemination of clinical trial synopses have been suggested as strategies to help overcome them.

Based on an analysis of the barriers to clinical trial enrollment and the emergence of the Internet as part of a new paradigm in healthcare information delivery, City of Hope National Medical Center was motivated to develop a Web-enabled database of oncology clinical trials information called Clinical Trials On-Line (CTOL). This report describes CTOL and the methods we have employed to assess its impact. A summary of the different types of interactions, inquiries, and outcomes generated by CTOL during its first 30 weeks of operation will be presented. The quantitative and qualitative data suggest that CTOL is capable of making a positive contribution toward increased clinical trial awareness and accrual.

1. Introduction

Advances in medicine and science are the result of new ideas and approaches developed through research [1]. Clinical trials are rigorous scientific experiments designed to evaluate new therapies in

human subjects while minimizing investigator bias, design flaws, and subjective evaluation of treatment data [2]. Since the clinical trials process is the most rigorous way of determining whether a cause and effect relationship exists between treatment and outcome, it is essential for understanding the effects of different cancer treatment approaches [3,4]. Many conclusions drawn from non-experimental data have led to years of unnecessary costly treatment and immeasurable suffering [5]. The efficacy of any new treatment that is to be accepted as the standard of care by the medical community must be established by evaluating it against the "state of the art" treatment in a well-conducted, randomized clinical trial [6,7].

A prerequisite for completion of a clinical trial is the accrual of enough patients to generate valid and reliable information about the effectiveness of new treatment regimens [8]. However, a significant factor limiting the availability of promising new therapies has been inadequate accrual of patients into clinical trials. Approximately 1.2 million patients are diagnosed with cancer in the United States each year, and 12-44% (144,000-528,000) of them are eligible for clinical trial enrollment [9]. Although surveys of the general public have shown widespread support for the concept of clinical trials, it is widely reported that only 1-3% (12,000-36,000) of patients diagnosed annually are enrolled [4-10].

Increasing the accrual of eligible patients into oncology clinical trials has the potential to decrease the overall mortality rate for cancer by [9,11]:

- Increasing the statistical power and generalizability of experimental results.
- Reducing clinical trial duration.
- Decreasing the time required to evaluate results, adopt new treatments, and generate new hypotheses.
- Reducing the risk of premature clinical trial termination due to inadequate enrollment and

subsequent loss of funding for the organization(s) conducting the trial(s).

- Improving the morale of patients and clinicians through increased confidence in the clinical trials process.
- Decreasing clinical trial workload, staffing requirements, administrative overhead and associated costs.

Many clinical trials contain interim analysis checkpoints to monitor for the appearance of statistically significant results that may warrant premature cessation of the study. It has therefore been suggested that even a modest increase in enrollment would allow most clinical trials to be completed in one year instead of the current 3-5 year timeframe [5]. This would also expedite conclusions drawn from longer-term follow-up studies, along with corresponding advances in cancer treatment.

2. Barriers to clinical trial enrollment

There are many barriers to the enrollment of patients into clinical trials. Physicians are generally aware of the importance of trial participation, but frequently do not know of trials available at nearby centers [4,12]. They also find it difficult to remember which clinical trials are active for a particular malignancy and the corresponding eligibility criteria [4,10]. These problems are exacerbated by paper-based information distribution methods that are known to be expensive, slow, and error-prone [12].

It is unusual for patients to initiate a discussion of clinical trials with physicians because their level of awareness about them is generally low [4]. Although physicians may be willing to allow their patients to participate, they often do not have the resources to identify eligible participants [4,11]. Additionally, the source of candidates for recruitment can dramatically influence the results if it does not include the requisite number and diversity of affected individuals. Many studies have relied primarily or exclusively on physicians, hospital records, or clinical laboratories for recruitment, and this approach is generally unsuccessful if used alone [11,13].

3. Strategies for eliminating enrollment barriers

There is widespread recognition of these barriers to clinical trial enrollment, and several strategies for minimizing them have been proposed. First and foremost is the need for increased public awareness

of and access to clinical trial information, accompanied by improved methods for its dissemination [6,9,12]. This information must be complimented by discussions with individuals who are well-informed about clinical trials and can answer any questions that arise [10]. The development and dissemination of synopses of active trials has also been identified as an important way to improve enrollment, along with the establishment of a toll free telephone number for inquiries and information requests [10].

4. Characteristics of healthcare information consumers

In addition to challenges that are specific to clinical trials, there are issues associated with the Internet and its impact on the evolving relationship between patients and physicians. There has been a growing movement advocating the view that patients are healthcare consumers with rights to information, interaction with health professionals, and participation in decision-making [14]. In particular, "baby boomer" and post-baby boomer patient populations are more autonomous, assertive, and demanding than patients of the past [15]. These patients demand second opinions, actively seek additional healthcare information, and possess an increasing level of medical sophistication [4,16].

Cancer patients actively seek the information they need to make rational decisions about treatment options, and are basing their decisions on various indicators such as National Cancer Institute (NCI) designations and specialized cancer research programs [4,15]. An increasing number of people in the United States are receiving healthcare from managed care organizations that have a financial disincentive to provide needed treatments, and many are concerned that they may be receiving cost-effective but suboptimal medical care [17]. Under these circumstances, patients and their families have a strong incentive to explore alternative sources of objective medical information.

Since the public is increasingly well-educated, curious, and used to seeking healthcare information from printed media, it is natural for them to turn to electronic sources of information such as the Internet [17]. Using the Internet, increasing numbers of healthcare providers and consumers are gaining access to an expanding volume of information that was previously inaccessible [18]. The tremendous public and professional demand for online cancer information is part of an emerging health care delivery paradigm in which information technology helps individuals to identify qualified consultants

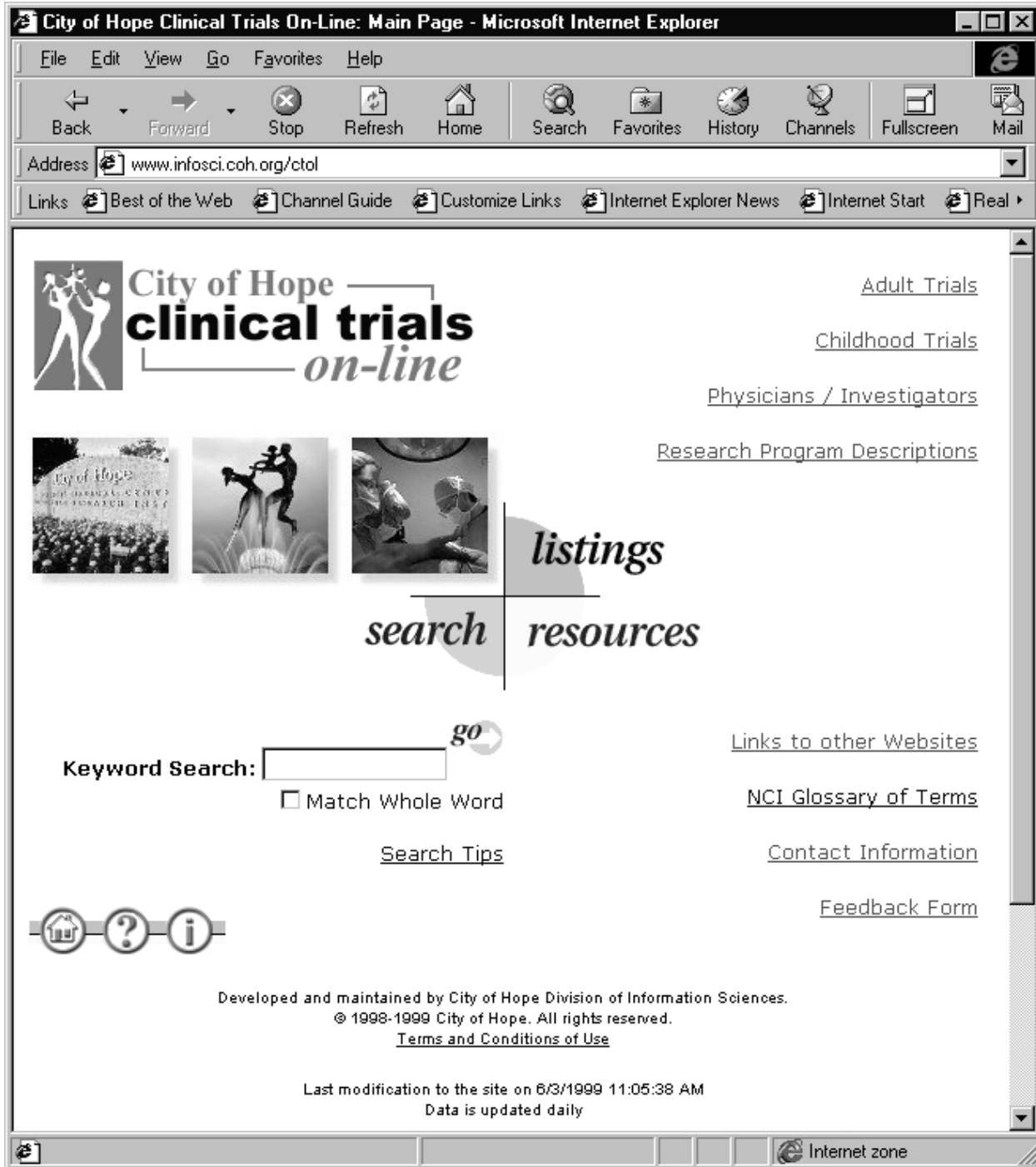


Figure 1. The City of Hope *Clinical Trials On-Line* home page.

outside their local healthcare system and to communicate with them directly [17,19].

Although several organizations have developed Internet-based information systems to distribute clinical trial information, many are limited by incomplete information, infrequent updates, and difficult user interfaces [12]. Based on an analysis of the barriers to clinical trial enrollment and the

emergence of the Internet as a widely-used source of medical information, City of Hope National Medical Center was motivated to develop a Web-enabled database of oncology clinical trials called *Clinical Trials On-Line (CTOL)*.

5. System and Methods

City of Hope National Medical Center, located in Duarte, California, is one of only 35 NCI-designated Comprehensive Cancer Centers, and is also a founding member of the National Comprehensive Cancer Network (NCCN). NCCN centers develop and institute standards for cancer treatment and perform outcomes research to ensure the delivery of high-quality, cost-effective services to cancer patients nationwide. *CTOL* was designed to describe City of Hope's research programs and ongoing cancer-related clinical trials to clinicians, patients, and the general public. The system currently contains descriptions of approximately 100 clinical trials, along with physician biographical information, research program descriptions, links to other websites, a glossary of terms from the NCI, and a mechanism for users to submit inquiries and feedback. The *CTOL* Internet home page is shown in Figure 1.

CTOL (<http://www.infosci.coh.org/ctol>) was developed by the City of Hope Division of Information Sciences. The Division consists of two departments: Biostatistics and Biomedical Informatics. The Biostatistics staff maintains a database of all information related to City of Hope clinical trials. The *CTOL* database is updated daily using exports from the Biostatistics Information Tracking System (BITS). The Biomedical Informatics staff designed and built the *CTOL* database and Web interfaces using Microsoft Active Server Page (ASP) technology and JavaScript, supported by Microsoft Internet Information Server (IIS) and SQL Server. The server hardware consists of two Dell PowerEdge 4300 Servers (400MHz CPU, 128Mb RAM). The IIS activity logs were analyzed by WebTrends (Portland, OR) to determine usage statistics for the website.

On December 31st, 1998 (because the development team promised to complete the system "by the end of the year"), *CTOL* was released on the City of Hope intranet for a two month beta test. The test period included many demonstrations of the system at department meetings across the organization, and an online survey that was announced repeatedly via e-mail and internal newsletters. The survey was completed by 42 City of Hope employees, and the results are shown in Figure 2.

At the end of the beta test, *CTOL* underwent minor modifications to implement changes and features suggested by internal users, and was subsequently deployed on the Internet on February 28, 1999. There has been an ongoing process of registering *CTOL* with Internet search engines and requesting

links on other medical information websites since its initial release.

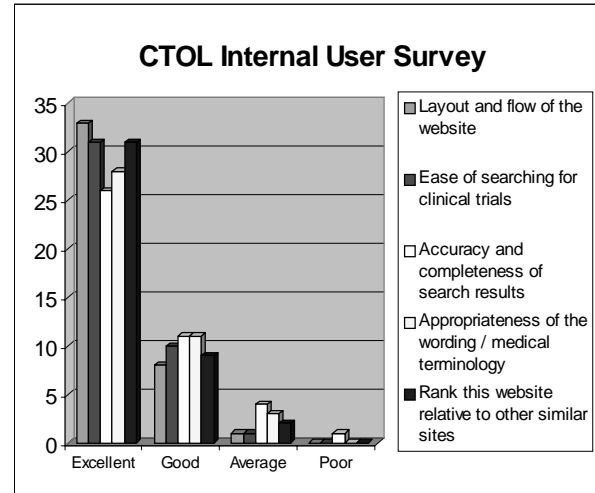


Figure 2. Results of CTOL internal user survey conducted during the beta test period. Rating categories are shown on the X-axis. The Y-axis shows the number of user responses in each category for each of the five survey questions.

6. CTOL features

CTOL can be used to identify oncology clinical trials by patient age category (adult or child), the physician conducting the trial, or by keyword search (i.e. drug name, side effect, etc). If age categories are used, the information is then sub-categorized by cancer type. All of the clinical trial information is dynamically generated from database queries. When a specific disease category is selected, the user receives a list of clinical trials that are open for accrual in that category.

When the details for a particular study are requested, *CTOL* presents a synopsis of the study that has been specifically designed for the lay public. An example is shown in Figure 3.

Each clinical trial summary provides a subset of the eligibility criteria along with a recommendation to contact City of Hope for additional information. All clinical trial synopses are reviewed and approved by the City of Hope Institutional Review Board (IRB). The composition of an IRB is multidisciplinary and includes non-medical health care professionals and lay persons from the community in addition to physicians and scientists [2]. The IRB assures that all human subjects research, including clinical trials, conforms with current ethical standards and all regulatory mandates.

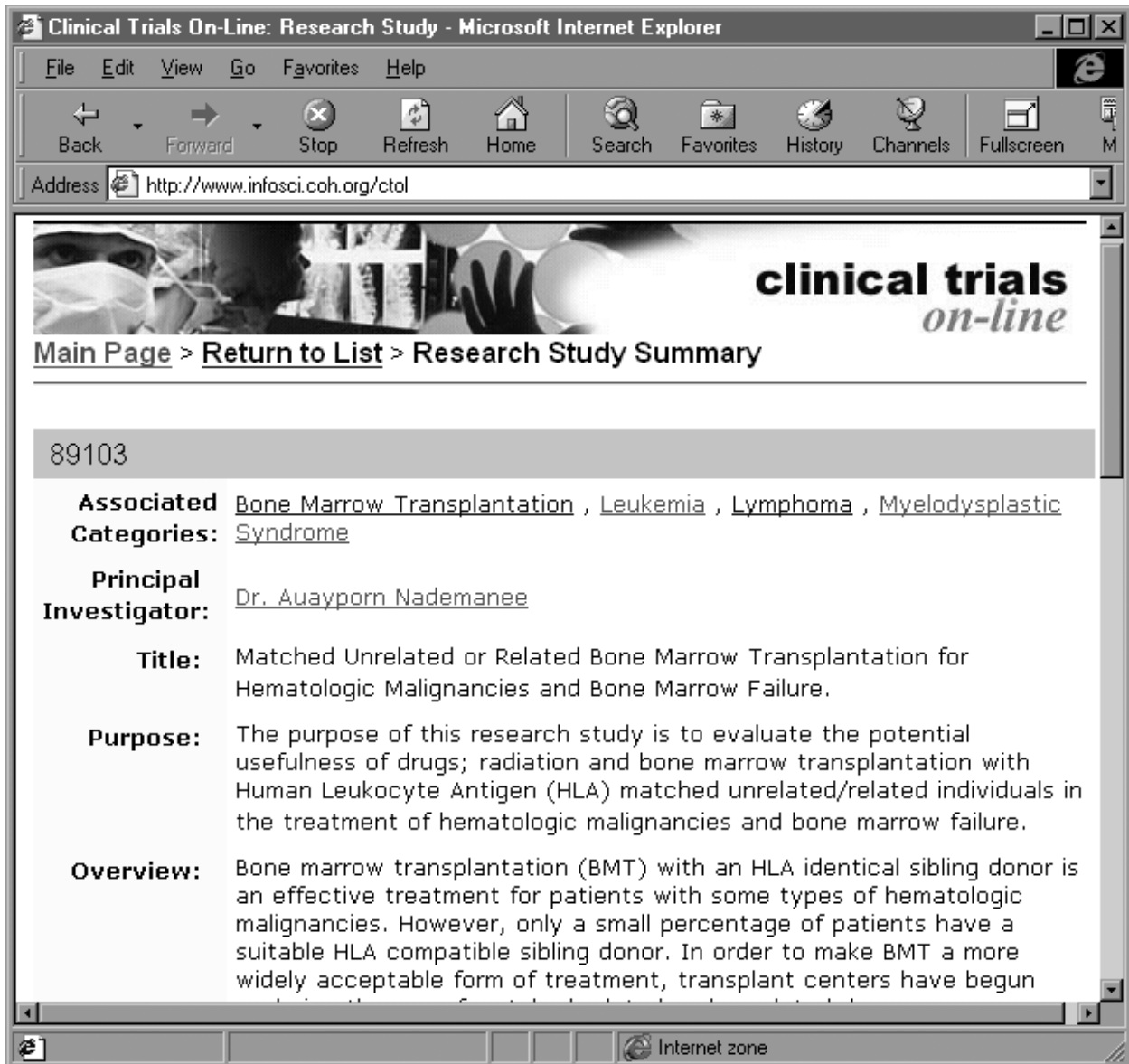


Figure 3. CTOL Lay summary of a specific clinical trial for childhood leukemia.

CTOL supports inquiries via fax, e-mail, and direct interaction with an inquiry database. The system also directs telephone inquiries to a call center staffed by trained professionals who triage patients, collect preliminary data, and provide additional information. The call center is a preferred mechanism for responding to information requests because it places users in direct contact with experts in the clinical trial process. However, telephone inquiries were not being linked to the system that initiated them. Since it is undesirable to interrogate potential new patients regarding whether or not they have seen a particular website, a more effective and less obtrusive information technology / telephony-based approach was developed to facilitate our evaluation.

To identify the number of call center inquiries generated by CTOL, a unique toll free number was placed in the contact information section of the website. Calls to this number are automatically forwarded to the call center, and call detail reports are used to determine the origin of the calls. Because this information is recorded transparently, it is no longer necessary for operators to ask if callers were referred by CTOL. This approach has been well received by the call center.

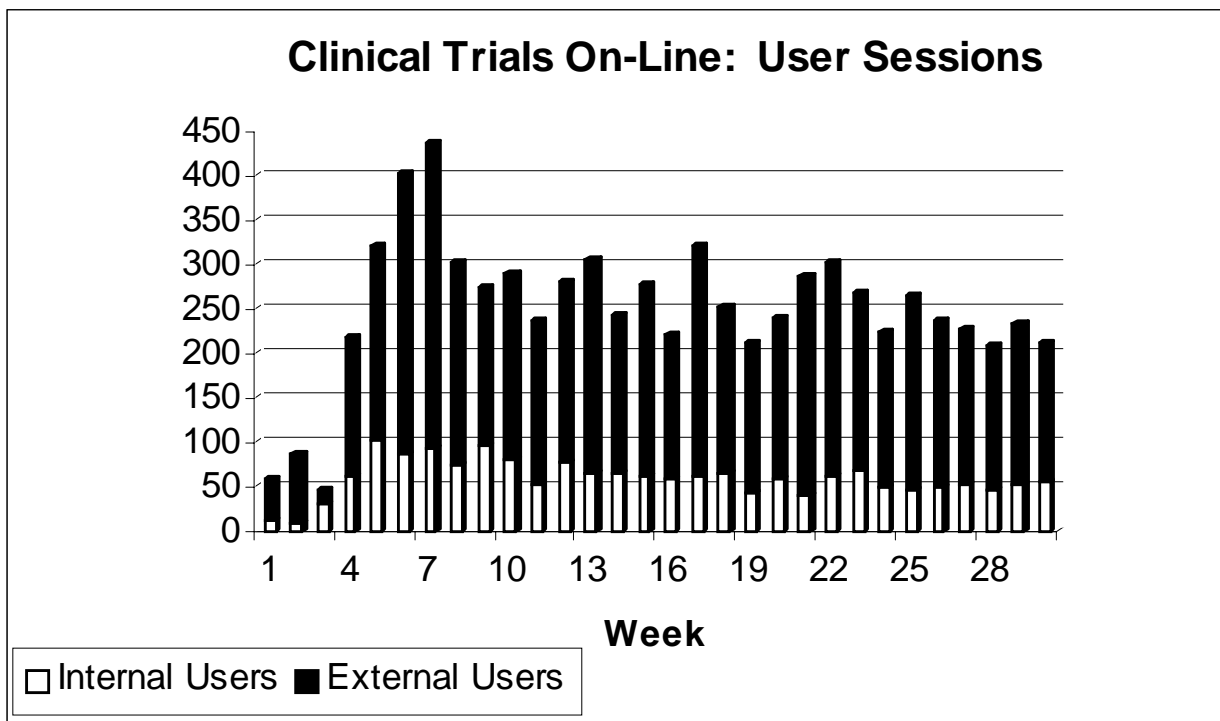


Figure 4. Thirty week summary of internal and external CTOL user sessions. Internal user sessions resulting from CTOL development and maintenance activities were removed prior to analysis.

7. Results for the 30-week operational period

To track usage patterns, a detailed log of all user interactions with CTOL was recorded by the Web server software and analyzed by WebTrends. The log contains Internet Protocol (IP) addresses, resources requested, and the time of the request. This transaction log is a very important and powerful aspect of information publishing via the Internet because it provides feedback required to evaluate the site’s impact [19]. During the 30-week period from February 28, 1999 to September 25, 1999 there were 7,452 user sessions recorded by the CTOL Web server.

A user session is synonymous with a “visit”, and is defined as a session of activity (all hits) for one user for a specified period of time [20]. An important distinction exists between user sessions and “hits”. A hit generally refers to the transfer of a specific object on a Web page. Therefore, as more clinical trials are added to CTOL, the number of hits generated per page will increase. User sessions provide a more reliable measure of site activity because they are independent of page complexity.

A more detailed analysis of the activity logs revealed that 24% (1,767 sessions) originated from

the City of Hope intranet, and the remaining 76% (5,685 sessions) originated from the Internet. The average user session length for CTOL is over seven minutes (7:06), indicating that users are spending enough time to interact with the site and peruse its contents. A summary of internal and external user sessions for the first 30-week period of operation is shown in Figure 4.

8. Internal CTOL user sessions

The City of Hope intranet is divided into more than 70 subnets that regulate the flow of network traffic between functional areas. These areas include departments that are physically located on the 100-acre main campus, and regional offices located in twelve North American cities. The web server activity logs were used to identify 14 subnets where CTOL was accessed 25 or more times during the 30-week deployment period. As expected, the two subnets with the highest activity levels were those supporting the departments of Biomedical Informatics and Biostatistics, corresponding with CTOL development activities. However, we were encouraged by the discovery of increased CTOL usage in several other functional areas as shown in Table 1. The initial increase in internal activity seen

Functional Areas in Subnet	Number of User Sessions
Marketing, Public Affairs, Patient Accounting, Health Education, Managed Care, Medical Staff Offices	570
Information Technology Services	159
Corporate Accounting	129
Development Center	126
Inpatient Hematology, Medical Oncology and Bone Marrow Oncology	118
Pediatrics, Hematology, Radioimmunotherapy	95
Clinical Pathology & Cytogenetics	55
Research Administration	52
New Patient Referrals	42
Physician Relations	36
Chicago Regional Office	32
Administrative Offices (Executive)	28

Table 1. Internal CTOL user sessions by functional area.

in weeks three through five (Figure 4) is believed to be the result of several articles about *CTOL* that were published in City of Hope internal newsletters.

9. External CTOL user sessions

Our analysis of Internet traffic to *CTOL* identified frequent inquiries from certain specific IP addresses corresponding to America Online, EarthLink, and WebTV™ Networks. Since many users of these resources share a small group of IP addresses through a security firewall or proxy server, they are consistently among the most frequently observed addresses in our transaction logs. Similar results have been reported for the Internet cancer information resource *OncoLink* [19].

We have identified *CTOL* user sessions from the National Library of Medicine, National Institutes of Health, National Childhood Cancer Foundation, National Breast Cancer Coalition, and most of the 17 NCCN cancer centers. There have also been many user sessions from universities, community hospitals, pharmaceutical companies, health maintenance organizations, insurance companies, news organizations, and international visitors in 42 different countries. These results are also consistent with those reported for *OncoLink*, albeit on a much smaller scale [19]. The steady increase in external activity in weeks four through seven (Figure 6) is believed to be the result of a message about *CTOL* (including a hyperlink to the website) sent to several cancer-related USENET news groups.

10. Summary of CTOL information requests

The most credible evidence to date of *CTOL*'s impact on clinical trial awareness is the direct feedback we have received from cancer patients and their families. To date, we have received 93 direct inquiries via e-mail and the *CTOL* online information request form. Of the 93 inquiries, 68 requested treatment advice and / or information about clinical trials. A summary of the user information requests is shown in Table 2. The results indicate that *CTOL* is becoming a valuable clinical tool and medium for information exchange. Another interesting finding is that physicians have started to use *CTOL* to communicate with each other and with patients about clinical trials.

In order to ascertain the impact of *CTOL* on clinical trial accrual, the City of Hope patient admitting system was cross-referenced with the *CTOL* inquiry database. Five patients were found in both databases. The medical record numbers for those five patients were then entered into BITS to determine if any of them had been enrolled into a clinical trial. We were extremely pleased to discover that one of the patients had been enrolled. A more detailed analysis revealed that the son of a woman with pancreatic cancer contacted City of Hope via *CTOL* in its 14th week of operation. After receiving a call from our call center, the woman was referred to City of Hope and enrolled into a clinical trial several weeks later.

The unique toll free telephone number for *CTOL*-generated inquiries was placed into service during the 11th week off the 30-week operating period. Since that time, the call center has received 33 calls with a cumulative duration of over 90 minutes. Nine calls were received from states other than California (AL,

Inquiries seeking treatment advice and / or information about clinical trials (relationship to patient)	Inquiries not related to clinical trial enrollment
<ul style="list-style-type: none"> • Self (20) • Parent (9) • Child (7) • Spouse (7) • Not specified (7) • Friend (5) • Other relative (5) • Sibling (4) • Physician - external (3) • Patient advocate(1) • Physician - internal (1) • Research scientist – internal (1) 	<ul style="list-style-type: none"> • Requests for additional information after seeing a news report / press release (7) • General questions and comments about City of Hope and cancer (5) • No specific request, but contact information provided (5) • Miscellaneous requests for information (4) • Requests for collaboration from other groups conducting clinical trials (3) • Current City of Hope patients seeking additional information (2) • Current / former City of Hope patients offering information / CTOL suggestions (2) • Vendor solicitations (1)
Total = 70	Total = 29

Table 2. Summary of information requests received from CTOL. (NOTE: six inquiries contained both clinical trial and non-clinical trial information requests).

CO, DC, IL, MT, NY, OH, PA, TX) and one was received outside the US (Canada). The remaining 23 calls were received from 13 different California cities. This suggests that CTOL can be credited with patient information requests other than those received directly via the Internet.

11. Lessons learned and directions for future research

Short-term objectives for the continued development and enhancement of CTOL include the addition of clinical trial information for diabetes, HIV / AIDS, and several other disease categories. As we add more information to the system, we also recognize the need to improve its retrieval features. Toward that end, we are experimenting with the new English Query facility in MS SQL Server 7.0 to provide a more robust natural language interface for querying the database [21]. We are also expanding the data model to include eligibility criteria for automated eligibility matching.

There will also be continuing efforts to register CTOL with search engines and Internet health information directories. A subscription service for regular automated search engine submissions was purchased in week six and has been surprisingly ineffective to date. Although our Web transaction logs show regular visits from search engine indexing “spiders”, only 1.1% of external users were referred by major Internet search engines (AltaVista, AOL NetFind, GoTo, LookSmart, Yahoo). Another 3.9% were referred by health information directory services (NCI cancerTrials, Health On the Net (HON), Achoo Healthcare Online, SciTalk.com).

The majority of external users (59.3%) are referred to CTOL directly from the City of Hope Internet home page.

The use of “push” technology is being explored for features such as automatic e-mail notification of clinicians and support groups about new clinical trials. We will also make corresponding changes to our WebTrends reports to analyze the usage of these new features as they are deployed.

CTOL currently supports both e-mail and direct submission to an inquiry database via an online information request form. We are planning to discourage the use of e-mail as a method of submitting information requests for the following reasons:

- The online form prompts users for specific contact information that is often not included in e-mail requests, while also providing comment fields for additional input.
- The online form places user inquiries directly into a database. In contrast, e-mail inquiries must be processed independently.
- Transactions with the online form can be protected using the Secure Sockets Layer (SSL) protocol supported by most Web browsers. This approach allows us to increase the security and confidentiality of sensitive patient information beyond that which is possible via e-mail.

12. Advantages and disadvantages of alternative approaches

The authors recognize that centralized Internet clinical trial listing services such as PDQ and

CenterWatch offer an alternative to *CTOL* for institutions that wish to disseminate clinical trial information online. One could argue that these services already exist, already contain references to many clinical trials being conducted across the US, already receive a considerable amount of Internet traffic, are more cost effective, and do not require Web or database development expertise. At face value, these may seem like arguments against the construction of an institution-specific system like *CTOL*. However, the alternatives are not mutually exclusive, and the centralized approach has several noteworthy disadvantages.

Our concerns about incomplete and infrequently updated information on centralized sites are supported by previous observations in the literature [12]. Another disadvantage is the inability to enrich centralized content with hyperlinks to physician profiles, research program descriptions, and other institution-specific information of interest. The most distinct disadvantage is the inability to study emerging mechanisms of interaction between suppliers and consumers of clinical trial information. Without the kinds of usage information presented in this study, the true efficacy of Internet clinical trial information dissemination would remain a mystery.

13. Conclusions

Clinical Trials On-Line was designed to minimize barriers to the enrollment of patients into oncology clinical trials by exploiting the Internet and its emerging role as a global medical information resource. Physicians can easily determine the number and diversity of oncology clinical trials that are open for accrual at City of Hope, along with summarized eligibility criteria and a convenient mechanism for contacting the institution to receive additional information. It is an efficient and effective method for disseminating clinical trial information to clinicians, patients, and the general public, and has reduced the time, cost, and error associated with paper-based information distribution.

Results from early use of *CTOL* are encouraging but must be considered preliminary in view of the short period of data collection. The relatively low number of eligibility inquiries and modest accrual impact is not surprising given the limited scope of deployment and the short evaluation period. However, we have demonstrated that our ability to transparently associate the route of inquiry with subsequent patient enrollment into clinical trials is crucial to our evaluation of *CTOL* effectiveness. The quantitative and qualitative data collected during our first 30 weeks suggest that *CTOL* is capable of

making a significant positive impact on clinical trial awareness and accrual.

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