

THE GOOD, THE BAD AND THE UGLY: E-MAIL IN CLINICAL TRIAL MANAGEMENT

A Survey of the Clinical Trial Environment and how an Innovative Email Management Tool can solve the Problems associated with the undocumented and informal nature of this means of communication

WHITEPAPER

by Dr. Allison F. Wren | The Wren Group | August 28, 2004



© 2003 ePeople, Inc. All Rights Reserved.

THE GOOD, THE BAD AND THE UGLY: E-MAIL IN CLINICAL TRIAL MANAGEMENT

A Survey of the Clinical Trial Environment and how an Innovative Email Management Tool can solve the Problems associated with the undocumented and informal nature of this means of communication

by Dr. Allison F. Wren

The Wren Group
3702, South Virginia Street
Suite G12, No 381
Reno NV 89502

August 28th, 2004

CONTENTS

Industries' reliance on email	3
Email and the management of clinical studies	5
Survey Methodology	10
Survey Results	11
The Solution – CTMail, an innovative email management tool	14
Conclusions	15

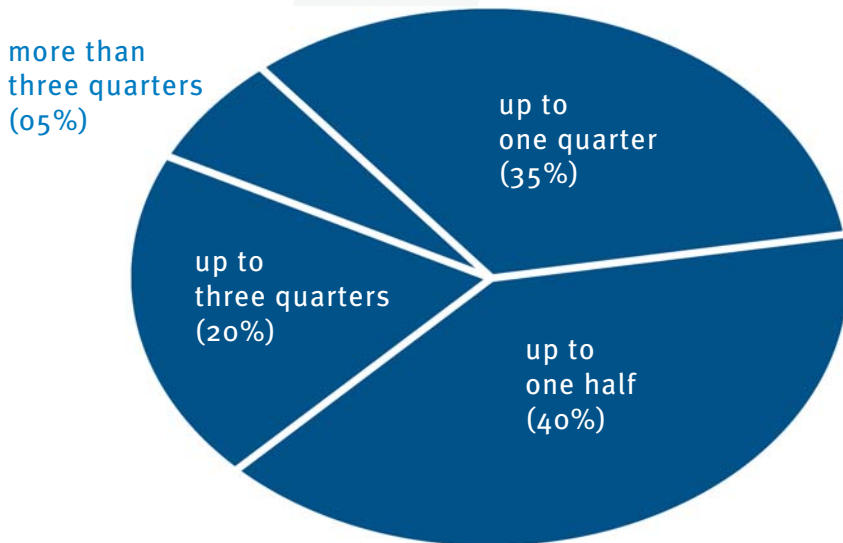
INDUSTRY'S RELIANCE UPON E-MAIL

Since the inception of the Internet, email has become so widely popular that it has replaced letters (now called "snail mail") and faxes as the preferred means of rapid business communication. Whilst some may deplore the quality of the writing within email with its reduced syntax, incorrect grammar and replacement of proper words with symbols and phonetics, this quick fire way of getting your message or query to all your colleagues has changed forever how we in the advanced world communicate. Even now, in the developing countries, the post man and his bag is being pushed out by the electronic age.

The growing familiarity with computers and their ability to allow attachments to these email messages opened up a second wave of enthusiasm for this method of communication. Now everybody could receive the spreadsheet, plan, photograph or diagram (many times whether they wanted it or not!) with a single click, overcoming the problems of distance and enhancing the effectiveness of teams. Thus email has become the de facto means of communication in the 21st century, both between single individuals as well as those in organizations tackling complex problems.

In a recent 2003 study, Kahn Consulting Inc conducted interviews with many 100s of employees across a broad swathe of industries in the USA. Figure 1 provides a breakdown of how many hours each individual spent in their "Inbox".

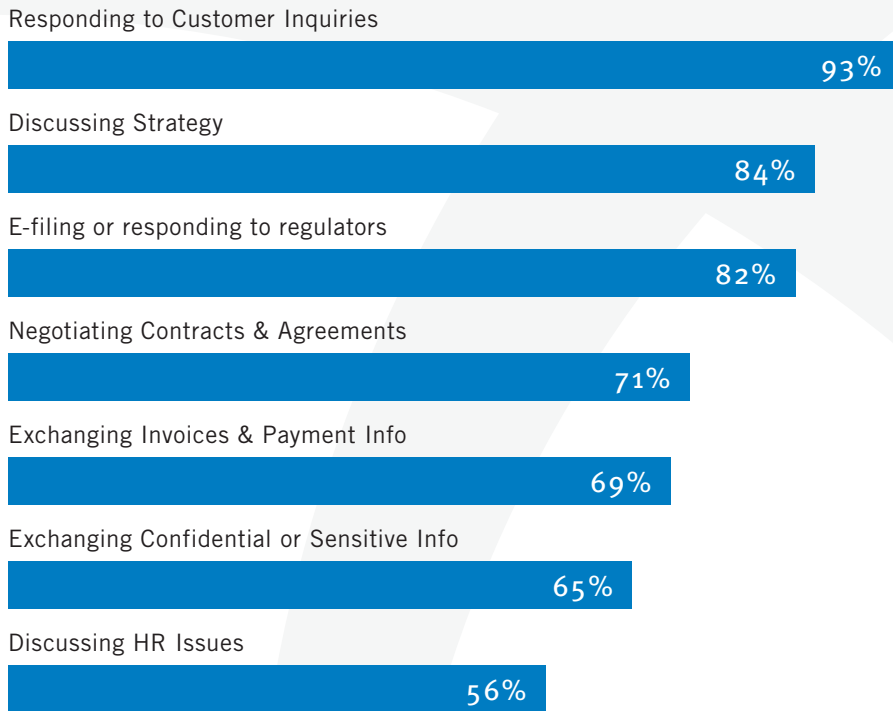
[Figure 1] Daily Time Spent on E-mail Tasks (as a percentage of respondents)



Source: *Managing E-mail in the New Business Reality*, AIIM International and Kahn Consulting, Inc., September 2003

Kahn reported a staggering 95% of respondents spending between 25 and 75% of each working day on email tasks. This varied between disciplines as shown in Figure 2.

[Figure 2] How Organizations Use E-mail Today (as a percentage of respondents)



Source: *Managing E-mail in the New Business Reality*, AIIM International and Kahn Consulting, Inc., September 2003

What was of particular interest, although not unexpected, was how much of the email was **associated with the transfer of controlled regulatory, sensitive and confidential information**. This, despite the increasing concerns about general lack of security and the now legendary ability of hackers to infiltrate even the most coded and encrypted programs. In fact, the complacency now associated with email is one of the problems that this paper will address. This arises from the essentially informal and conversational mode of email compared to a controlled document or data package in either electronic form or hard copy.

In a 2003 KRC study, industry wide respondents reported that **45% used email twice as much as the telephone**. Yet another investigation, published in November of that year by Gartner, reported that as much as **75% of knowledge sharing is now done via e-mail**. This despite the fact that each correspondent's personal folder filing systems is unique and incompatible with everyone else's on the team. Little thought has been given to this problem, although rapid information sharing has been at the root of the increased productivity experienced by western organizations over the last 20 years.

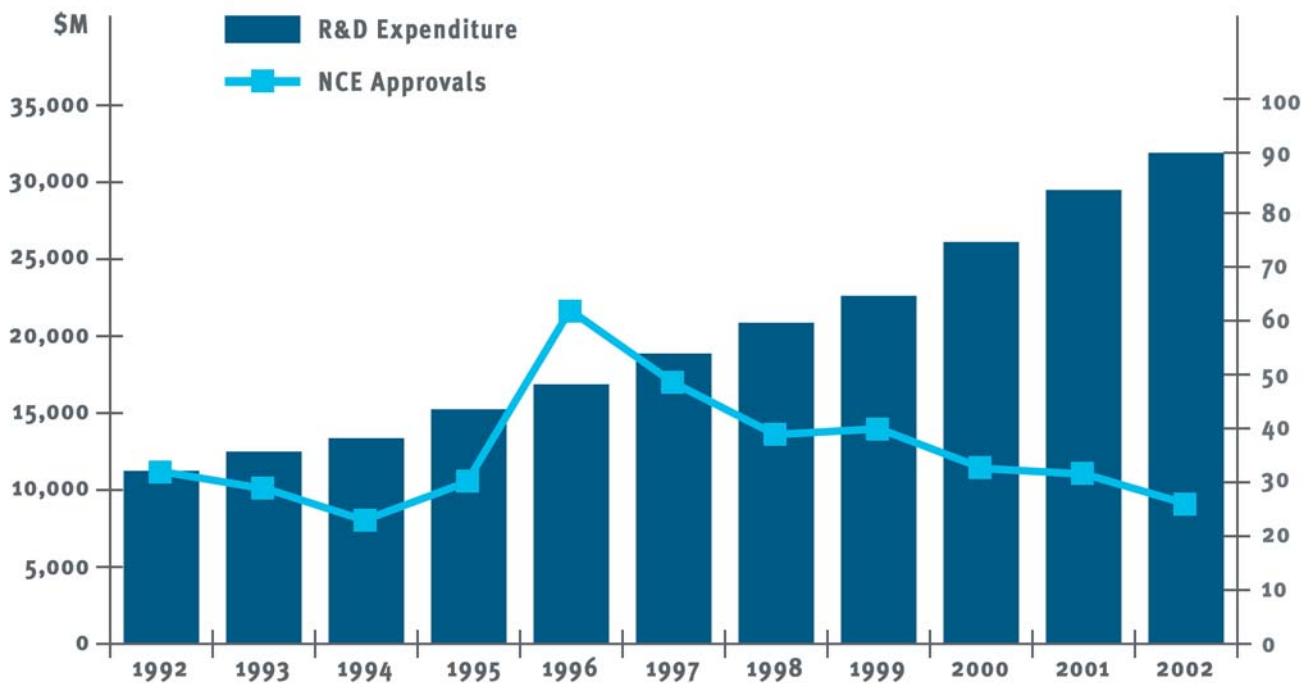
Given this widespread use of electronic mail, with its advantages of speed and accuracy and the easy sharing of documents, it is no surprise that this medium has been adopted as the chosen way of managing the

complex world of product development in all commercial and research disciplines. This paper will describe its use in the highly regulated world of clinical trials and how it has become both a boon and a liability in this field.

E-MAIL AND THE MANAGEMENT OF CLINICAL STUDIES

Increasing regulatory requirements and burgeoning pharmaceutical research has resulted in a huge growth of drugs undergoing clinical trials. The pharmaceutical and biotechnology industries now **spend ~\$35B in the US alone**, despite the fact that these investments are not resulting in as many new chemical entities as in previous years (see Figure 3). The latest figures from the Pharmaceutical research and Manufacturing Association (PhRMA) indicate that these are falling to record low numbers.

[Figure 3] PhRMA Members R&D Expenditure vs. NME Approvals (1999 2002)



Another important industry statistic is the fact that the final phases of product development – the clinical trials in human volunteers and patients – consume an increasing proportion of the overall R&D funds. BCC Research, in a 2004 report, calculated that approximately **50% of the total R&D expenditure on a successful drug is spent on the clinical testing phase**. In 2007 this alone is forecasted to amount to \$26B. Figure 4 and Table 5 provide some information on this from the BCC report

[Table 1] Total Product Development and Clinical Trial Research Spending in \$M

TOP 10 PHARMACUETICAL COMPANIES IN ORDER OF TOTAL REVENUES	R&D BUDGETED	ESTIMATED RANGE OF CLINICAL TRIAL COSTS*
Pfizer	4,847	1,454 to 3,393
Merck	2,456	737 to 1,719
Johnson & Johnson	3,591	1,077 to 2,512
Bristol-Myers Squibb	2,259	678 to 1,581
Pharmacia	2,263	679 to 1,584
Eli Lilly	2,235	671 to 1,565
Wyeth	1,869	561 to 1,308
Schering-Plough	1,312	394 to 918
Abbott Laboratories	1,578	473 to 1,105
Baxter	427	128 to 299

[Figure 4] US Pharmaceutical and Biotech Industries' Clinical Research Spending

These enormous numbers underpin the importance to the pharmaceutical industry of clinical testing, since around 90% of drugs that enter the final Phase III trial will eventually receive FDA approval.

The Clinical Trial Process Must Become More Efficient

The growing complexity of the clinical trial field has been the result of many different pressures for change:

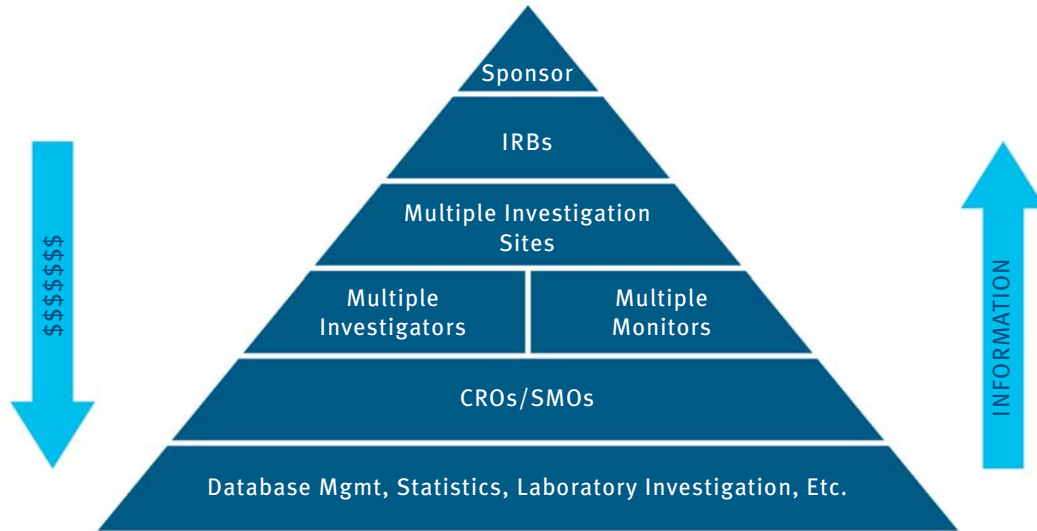
- **Increased competition for subjects and investigators**
 - Large trials widely dispersed geographically over many sites
 - Influx of new Clinical investigators
 - Principal investigators remote to sites
- **Increased need for speed**
 - Remote data collection and electronic transmission
 - Central IRBs and study monitoring
- **Increased reliance on contractors (e.g. CROs/SMOs)**
 - Greater fragmentation in dispersing study functions

-
- An SMO means a person or organization that assumes, as an **independent contractor with the clinical investigator**, one or more of the regulatory obligations of a clinical investigator, e.g., preparation and maintenance of case histories, ensuring compliance with IRB review and informed consent requirements, Adverse Event (AE) reporting etc.

-
- A CRO means a person or organization that assumes, as an **independent contractor with the sponsor, one or more of the obligations of a sponsor**, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the FDA.
 - To the extent that an SMO meets this definition it would be considered a CRO

This has fed the use of email as really the only method of communication that can encompass these changes and still bring some aspects of efficiency and control. However, as our research has shown, both these seeming attributes are under threat as the trial monitors and co-coordinators struggle to manage an ever engulfing flow of time-sensitive and often confidential data. Completely new employment categories have joined the established position of Clinical Research Associate (CRA). These include Clinical Research Monitors/Co-coordinators/Scientists as well as the new Clinical Research Organizations (CROs) and Site Management Organizations (SMOs). Couple this with the Sponsors, the Institutional Review Boards (IRBs), all the clinical investigators, researchers, manufacturers of the clinical supplies, the hospital and clinic coordinators and it is easy to see how email has become ubiquitous within clinical trials. This is shown pictorially in Figure 5.

[Figure 5] Complexity of the Product Trials



CRO Service Quality Impacted by Responsiveness and Employee Turnover

In September 2003 CenterWatch reported on its biannual survey of the relationships between investigative sites and the CROs that manage the trials. There had been little change since 2001 when 40% of all site respondents said that they were either neutral about the quality of the interaction or that it was only poor to fair. Of the 396 respondents to the 2003 survey, 7 out of 10 rated “Responsiveness to Enquiries” and “Maintaining Open Communication” as essential to a successful relationship. However only 25% reported that they were satisfied with the general “Professionalism” of the CROs. This category included an assessment of the communications between CROs and the sites. Overall the CROs were considered less responsive, less organized and less open to maintaining channels of communication than trial sponsors. A perennial problem for all participants in a trial – but especially the clinical sites – is monitor turnover. Nearly two out of three CRAs will change positions within a 2 year period. Further, approximately half of all sponsor-employed CRAs will change jobs within that same period. This constant turnover is dragging down study efficiency and increasing the already astronomical costs of clinical drug and medical device testing.

Clinical Trials Subject to Heightened Regulatory Environment

Along with this complicated flow of information and payments, is an increasing regulatory oversight. The Sarbanes-Oxley Act has changed how we think of and our relationship to electronic communication:

- All records (including electronic) created, sent or received in the course of an audit MUST be retained for seven years
 - includes working papers which contain conclusions, opinions, analysis or financial data related to an audit
- E-mail is no exception and is viewed as a major liability, managing it better is the cost of staying in business
- According to Gartner (2003) *“most enterprises should take a step further than ‘just complying.’ If the enterprise must comply in any case, why not do it proactively and adopt a culture of information democracy?”*

The FDA has recently been much more proactive in requesting email communication during trial audits or examinations of both pharmaceutical sponsors as well as CROs. However the industry has neither received nor created any guidelines about how to record, document and archive email.

The Role of E-mail in Clinical Trials

There is little research available on how email is currently used in the clinical testing process and whether any standard operating procedures governing its use have been developed. How would compliance be assured? Another important question is whether email use really does improve clinical trial management or whether it actually hinders productivity by placing important information in the personal files of every participant rather than enabling it to be shared between all those involved in the study? A third query is whether email could be used to enhance relationships between trial sponsors, the study monitors and their investigative sites which, as we have seen from the data above, is in a somewhat parlous state? Based on a recent study by the Philadelphia College of Science, 38% of investigators were more likely to prescribe a drug based on having positive experiences with the preceding study as compared with those that had negative experiences. Therefore, the manner in which the trial is conducted is an important, early investment in future product success.

Other avenues of questions surround the compatibility of email with Clinical trial management system (CTMS) and Electronic Data Capture (EDC) software that are now widely used in the industry. These conventional management systems do not include email resulting in confusion over just what constitutes a controlled document and whether it should be archived as part of the clinical record, passed to others or deleted. As Bob Evans, Editor-in-Chief, Information Week wrote in July 2002 *“First, the power of information is in its visibility and thereby its ability to be leveraged, enhanced, and acted upon; and second . . . business-technology managers today have to hold themselves accountable for getting the information out to the places where it can be most effective.”*

In an attempt to answer these questions, ePeople, a leading provider of business email management solutions for high-value customer relationships in Life Sciences, High Technology and Engineer-to-order industries conducted a 4-month study within the broad clinical testing environment. Currently ePeople's solutions for collaborative support and team selling (CRM software), streamline complex processes that demand close coordination of experts, best practices and knowledge. The company believes that its technology is ideal for managing email within another collaborative environment. In order to customize its technology to the new arena of clinical testing it needed to fully understand the complex flow of email between the participants as well as what information is critical to each level of management. In addition, the acute timing requirements of a well-managed clinical trial demand a foolproof system of alerts, something that ePeople's technology can easily encompass.

THE SURVEY METHODOLOGY

Telephone conversations, the exchange of emails and face to face meetings were conducted, according to a standard protocol, with all levels of stake holders within the clinical testing field as shown below. In total 116 contacts were made and documented:

- Pharmaceutical companies, large and small -18
- Medical Device Companies - 4
- Biotechs, large and small - 5
- CROs -10
- SMOs - 5
- Research Hospitals and clinics - 6
- CRAs and Study Managers - 48
- Clinical Investigators -16
- Professional Organizations - 3

The questions covered all aspects of the use of email, from how many messages were received in a week to the time taken to respond to these and manage (cutting and pasting) their content and attached documents, from how much information could be missed by the personal nature of everyone's email filing system to the nature of the email content and its sensitivity and importance to the outcome of the trial. We also requested information on the relationship of the contact with the FDA and whether this Agency had requested any email communication as part of an audit. Information was requested on which aspects of the trial communications stream most contributed to the success of the study, both locally and to the trial as a whole and when problems arose, what solutions had been developed in house or in collaboration with other participants.

Conversations were held with Clinical Research, Regulatory Affairs and Medical Directors, Clinical Research Managers and Monitors, CRAs, CRCs, Directors of Hospital and Clinic Protocol and Research Groups, senior members of professional organizations representing the industry, consultants and clinical investigators at large and small hospitals in a focused examination of how email is used by them all in the monitoring and supervision of clinical trials.

SURVEY RESULTS

The first part of the investigation focused on how email is used by survey respondents in their daily administration of a clinical trial.

We found strong agreement with the industry wide survey mentioned at the beginning of the paper with ~70% of the working week of a CRA spent dealing with email. *"Up to 90% of my day is spent organizing and searching for information and documents in email"* reported a Senior Clinical Research Scientist, in an F500 Pharmaceutical Company.

- CRAs manage ~**1000** emails every week
- CRAs spend **60%** of their working week inside the inbox
- CRAs spend **10%** of their working week searching trial email
- CRAs manage emails locally in personal files & folders
- No access to data for site auditing and monitoring is ad-hoc

Thus all of the critical information, from patient recruitment and drop out, to adverse event reporting and payment requests, are within the soft, uncontrolled environment of email, subject to each individual's personal filing and folder system. It is not possible for managers to get access to the data held on their CRAs' computers, forcing them to rely upon weekly reports which may or may not be completely reliable. In addition, a CRA may monitor up to 20 trials and/or 20 clinical sites and spend hours cutting and pasting information to site and trial-specific data stores..

Additional information from a major research hospital's Clinical Trial Office provided similar information about the complexity of the trial environment:

- Currently it has **2244** active clinical protocols managed in email
- Since 1984 the hospital has created **8000** clinical study protocols
- **All** emails from all trials are archived
- All emails are tagged by trial names & numbers
- They use email to manage **~1000** adverse events each month
- Typically over **200 email threads** stored per protocol in email
- Frequently accessed by staff, IRBs, Sponsors and by the FDA

As the above listing indicates, this hospital had realized that it had problems with documenting all the data within email and in 1998 developed in house software in which the email database is the regulatory management system for the whole clinical testing program. This was a powerful validation of ePeople's premise that email within clinical trials needs to be managed in such a way that assists in the completion of the clinical record as well as making the participants more productive. Much of the CRA's time is spend checking that all the documents associated with the trial have been completed satisfactorily and properly controlled, according to the Standard Operating Procedures (SOPs). Failure here results in a lengthy Quality Assurance (QA) period before data lock down with its accompanying fear of an audit that might uncover non compliances. As the VP Regulatory Affairs of a small pharmaceutical company said, "Quality Assurance and Regulatory Affairs could benefit from improved and managed email communications within our clinical team".

The primary problems with e-mail can be summarized in the following 5 points:

- 1. Inadequate management and processing of email information** from the sites, CRAs, monitors and investigators to the sponsors, CROs etc. The knowledge is locked in personal files and folders, requiring endless cutting and pasting. This was the most often stated problem, followed by the delays to productivity and mistakes that follow the frequent change of monitoring personnel.
- 2. Lack of management access to essential and often critical study and site information.** For example, the mention of a possible unexpected AE within the body of an email might not be noticed by monitor or copied to other interested parties in real time.
- 3. Email communication inefficiencies lead to delayed decision-making by senior management.** It has been estimated that every day in a 1000 patient pivotal Phase III study may cost the sponsor > \$100,000. Decision makers have no way to measure the responsiveness of various groups nor the progress being made on critical issues
- 4. Inability to merge information contained in email with the CTMS and EDC software.** Managers were

frustrated with the ad hoc and inefficient processes adopted by each monitor.

5. Potential for serious noncompliance with regulatory requirements especially since there are currently no guidelines available. There is little standardization of process among employees, contractors, outside vendors and the best, indeed valiant, efforts of the monitors are again cutting and pasting into their personal filing system. From the study only two percent of respondents had formal email compliance policies. One large pharmaceutical company had established a recent policy of only using the telephone and a written reporting system to monitor trials and investigate problems, such was its concern about future liability and unpleasant surprises surfacing in email.

The second part of the investigation requested information on what an email management system should look like on the desktop, how it should interact with the user's other software, browsers, etc as well as how user friendly it has to be. Most importantly, all respondents insisted that the solution should not require any extra effort from the monitors or the investigators in its daily use. Other suggestions for the system included the ability to:

- Capture events and useful comments early, leading to better decision-making and progress
- Provide a real time overlook of a study for managers
- Operate in the background so as not to be intrusive in a world where data collection and reporting is understood and accepted
- Provide mechanisms to efficiently communicate and improve relationships with investigators with timely and complete information and successful attainment of clinical trial milestones
- Improve coordination of efforts among investigators, monitors, clinical researchers, and regulatory experts to streamline site management and reduce trial delays.
- Improve knowledge transfer between study phases and between personnel
- Offer rapid access to a particular history in a well organized and clear fashion
- Be customizable by user role or specific requirements of the trial
- Alert users to a possible problem, such as low patient enrollment as well as to the need to file a document or request supplies.

Email is not going to “go away”, despite one of our interviewees indicating that it had now banned its use in all company clinical trial interactions. We have this love/hate relationship with the medium since it is easier to approach certain topics in an informal but still knowledgeable way rather than create formal documents that have no clear home in the system.

This basic dichotomy facing all of us who regularly use email in our working lives was summed up well by Anthony Lye, CEO of ePeople, in an August 16th interview with Mark Uehling of Bio-IT World/eClinique, an online magazine monitoring the progress of clinical trial technologies. In a conversation about how the current CTMS systems fail to capture email, Lye commented that *“But there are other situations in which an asynchronous conversation (i.e., an email) is better and more satisfactory. In these situations, even the best CTMS is of limited value. Where those systems break down is where email takes up the slack, where you can't define a problem simply, and you want it to have a conversation about it.”* This gets to the heart of the problems expressed by our survey respondents.

THE SOLUTION – CTMAIL, AN INNOVATIVE E-MAIL MANAGEMENT TOOL

ePeople's CTMail is an email management solution for clinical trials that establishes strong investigator relationships by streamlining communication and centralizing information among all study participants, managing expertise, and providing collaborative workspaces to react faster to and efficiently resolve study issues. It saves the monitor's time and energy that can be better spent on problem solving rather than cutting and pasting and ensures that managers can check the progress of every aspect of the trial at a glance.

CTMail is an innovative email management tool designed to transform how email is used to manage daily activities and provide management with the visibility they need to make time-sensitive decisions. CTMail eliminates the daily grind of email for the CRA since their clerical efforts are now replaced with a set of new collaborative capabilities that link experts, knowledge and best practices across all clinical trial participants. CTMail is embedded within the familiar email client and consistent with today's email work practices.

CTMail automatically categorizes each message with XML tags based on the content of the message. Users can also manually assign the tags or remove them from an individual email. These tags organize the content of the email, which can be sorted and reviewed according to a user's privileges. All this is done using the familiar Outlook dashboard and requires little action from the monitor. CTMail has been carefully developed to restrict the menus to only meaningful categories, removing confusing terminology and unnecessary links, thus ensuring a simple user experience.

Table 2 summarizes how CTMail address the challenges identified with email in the study to delivers a powerful solution to better manage sites and accelerate the overall clinical trial process.

[Table 2]

REQUIREMENT	CTMAIL	COMMENTS
Manage knowledge	Maintains accessible central store of original email threads identified by XML tag	Searchable, auditable Database, no more need for cutting and pasting
Generate Alerts	Time based alerts and calendars	Customizable to every user for individual site/trial tasks
Transfer knowledge between CRAs and phases of a single trial	New personnel simply review all the email threads and attached documents that describe every aspect of the trial	Increase productivity and reduce down time and mistakes due to learning curve of new monitors
Obtain expertise outside of specific group	Easy to add extra persons to a thread, even those outside the trial team	Faster problem resolution
Allow experts to participate with any messaging device	This includes cell phones, text pagers, or PDAs	Greater productivity
Assign and manage tasks	Menus allow for identification of person responsible for next action	Efficient progress and easier management oversight
Search a central email repository	Powerful search features covering every aspect of the trial	Fully customizable for every level of participant
Operate Securely	Completely secure	Trial confidentiality maintained
Maintain CFR 21 compliance	Yes	Anticipates FDA and other audits

Handle Attached Documents	Links relevant documents to email threads in searchable database	Complete transcripts always available to all participants
Organize issues with an easy to use workspace	A portal-style workspace with every thread clearly identified in the Outlook format	Greater collaboration between participants, little training required
Compatible with all web browsers and email applications	Yes, with all	Users do not have to recognize and learn another inbox
Manage critical issues	Customizable menus which follow each thread associated with a specific task or problem	Management can assess team responsiveness and monitor key metrics
Install in a short period of time	A fully deployed system can be delivered in weeks	A measurable and immediate improvement in productivity
Reduce clinical testing costs	Saving at least 10% of a CRA's time as no more need to cut and paste, search and file	Enhanced overall productivity and efficiency of documentation

CONCLUSIONS

Email is the de facto method of communication between all participants in clinical trials of drugs and medical devices. However, the recent round of financial scandals involving lack of transparency of decision making, resulting in the Sarbanes-Oxley Act, as well as an increased FDA oversight of email is causing alarm within the pharmaceutical industry. How can this informal, conversational medium be controlled and become an asset within the regulated clinical study environment?

A survey of over 100 clinical trial sponsors, site investigators, CRAs and other monitors and trial managers resulted in a wealth of information about how they use email, their concerns and key requirements of an email management system. Using this information ePeople has developed a powerful clinical trial system that resides in Microsoft Outlook and provides a full range of activities that CRAs and trial monitors need to be more efficient and productive as well promote better relationships with clinical site investigators.

These activities include:

- Consistently manage issues from multiple site/studies
- Accessing important study documents from a central repository
- Identifying relevant experts and their availability
- Resolving issues across multiple organizations
- Identifying important information in long email strings
- Isolating, classifying and organizing important information and documents

ABOUT ePEOPLE

ePeople is a leading provider of business email management solutions for high-value customer relationships in Life Sciences, High Technology and Engineer-to-order industries. ePeople's solutions for clinical trial management, collaborative support and team selling, streamline complex process that demand close coordination of experts, best practices and knowledge. ePeople solutions are designed for rapid adoption and integrate with Microsoft Outlook, CRM, email, IM and the web. ePeople customers, including companies such as Cisco Systems, Pria Diagnostics, Cognos, Network Appliance, InstallShield, and Openwave Systems, enjoy significant gains in productivity, responsiveness and service quality. Headquartered in Mountain View, Calif., ePeople is privately held.

For more information on ePeople please call 650-694-6400 or navigate to www.epeople.com.

Corporate Office:

ePeople, Inc.
450 National Avenue
Mountain View , CA 94043-2388
Phone: 650.694.6400
Fax: 650.694.6401
Web site: www.epeople.com