Trust and clinical research

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Trust is an essential feature of clinical research. Participants must trust researchers to act competently and with their best interests in mind. Researchers must trust one another to carry out their roles as determined by the protocol and according to the standards of best practice. Clinicians must trust that the results are reported accurately and completely. The public must trust that the whole enterprise is conducted appropriately and to the highest standards possible. However, there are concerns that trust may be waning, particularly public trust in clinical research. The media have reported on events ranging from controversies, problems, and fraud in clinical research. Numerous polls report on growing public mistrust of research. "Gone is the time when government and the public unhesitatingly trusted research institutions to serve as responsible advocates of the public welfare." Research institutes are now searching for ways to restore and retain public trust and confidence in clinical research.

Key words: clinical trials, public confidence, trust

The Association of Clinical Research Professionals (ACRP) published a special issue of its journal, The Monitor, on measuring trust in clinical trials. Those articles will be reviewed here, along with an exploration of some related writing on the issue. As the director of ACRP noted, earning the trust of the public is a multi-faceted process. Central to the goal of building trust is “that clinical research is performed responsibly, ethically, and professionally everywhere in the world.”

Looking at trust

Trust is one of those concepts that we frequently talk about, but can be difficult to define. Clifford C. Scharke defined trust as “that strength or truth in which confidence is placed,” and confidence as “that sense of one’s abilities or ability to rely on that which is trusted.” In the context of clinical research, Scharke holds that trust is a sense that allows people to have sufficient confidence to consider participating as research subjects. This association leads to an assumption that the extent of public participation in research is a measure of the public’s trust in clinical research. Studies finding low and diminishing public participation in research are thus taken as evidence of loss of trust in clinical research.

However, trust is a more complex and elusive concept. Onora O’Neill is a British philosopher who has examined trust in detail in the context of biomedical research and bioethics. She notes that in spite of the importance of trust in medicine and biomedical research, it has received little in-depth analysis. Much of this she traces to the emphasis on autonomy and individual rights in Western bioethics.

O’Neill’s work builds upon the apparently anomalous nature of trust, where sometimes we trust those who have not been trustworthy and sometimes we misplace mistrust. This is because “trust is not directed to natural processes (however reliable) but only to other agents.” Trust and mistrust always have to do with relationships, which have important implications for how trust is retain or restored. “Trust is most readily placed in others whom we can rely on to take our interests into account, to fulfill their roles, to keep their part in bargains…. Trust flourishes between those who are linked to one another;…. Trust belongs with relationships and (mutual) obligations.”

The relational and ethical components of trust must be kept in mind as the more practical implications of trust in clinical research are examined. “The conduct of human research is not a right, but a societal privilege, conditioned on ethics and trust.”

Loss of trust

Kenneth A. Getz presented the results of several public opinion polls that he provided as evidence of falling public trust and confidence in clinical research. The percentage of those who would be willing to participate in clinical trials has dropped
consistently, from 63% in 2001, to 55% in 2004, and then 41% of white adults and 28% of minority adults in 2007. At the same time, between 2000 and 2006, patient recruitment rates fell from 75% to 59%. The average number of patients needed per trial has grown from 1,700 to 4,000 over the past 20 years, with 80% of trials being delayed because of enrollment difficulties. This has important practical consequences. In response to lower enrollment, research sites and sponsors are investing more funding into patient recruitment programs. Even while recruitment rates were dropping, spending on recruitment increased 12-14% annually.

Trust in those who oversee, manage, fund and regulate research also has been diminishing. A 2004 Harris poll found that 56% of Americans believed FDA was effective in ensuring safety, while in 2006 this had dropped to 31%. Another poll in 1997 found that 19% rated pharmaceutical and biotechnology companies poorly for failing to serve consumers, but this had increased to 39% in 2007. In 2008, 27% of Americans reported they did not trust pharmaceutical and biotechnology companies to give reliable information on drug safety or side effects. In another 2008 survey, half of white respondents and three-quarters of minority respondents replied that they thought it was “very likely” or “somewhat likely” that they would be used as guinea pigs in research without their consent.

One of the more surprising results revealed by such polls is a poor perception of research participants. Several studies in different countries have found that “a large percentage of the public considers research subjects to be risk takers who are motivated to find clinical trials because they are either greedy or desperately ill.” A 2006 Center for Information and Study on Clinical Research Participation (CISCRP) poll found that one-third of Americans “do not admire” people who volunteer for clinical research.

However, the data are not consistent across all diseases and populations. For example, more than 60% of children with cancer are enrolled in a clinical study, although only 5% of all cancer patients participate in a trial.

In spite of the above results, Getz reported on several other polls that indicate that the public remains positive in its belief that clinical research is important to advance medical knowledge and improve public health. One poll found that more than half of Americans wanted more money spent on medical research and two-thirds would be willing to pay $1 more per week in taxes to fund the research. Other polls in Western Europe show similarly positive attitudes among the public. Such anomalous findings about trust in several contexts lead O’Neill to ask whether the alleged crisis of trust should more accurately be described as a culture of suspicion. Rather than mistrusting clinical research in general, people are more suspicious about engaging with the enterprise personally.

Sources of distrust

According to Diane Simmons, many issues have led to erosion of confidence in clinical research. These include harms to patients and widespread media coverage of problems and misconduct in the industry. Participants have died during clinical trials, including healthy volunteers. Researchers have been caught reporting false or misleading results. High-profile, peer-reviewed journals have published fabricated data without being able to detect problems. Conflicts of interest have influenced the publication of results. Data has been selectively chosen to present a biased perspective on the efficacy or safety of an intervention. Heavily marketed pharmaceuticals have been withdrawn after being approved by all the necessary regulatory agencies. Participants have reported being coerced into studies.

The list of unethical and inappropriate practices could go on. Admittedly, high-profile media attention to individual situations cannot be taken as an overall reflection of the thousands of studies being conducted appropriately. To date, Mark Yarborough claims that the response to the negative media attention has been driven by regulators and a concern for compliance. However, in 2002, he warned that if research institutions did not address issues of trust beyond compliance with federal regulations “investigators may find it more difficult to recruit participants for their studies, and federal oversight of research may become more burdensome. Such developments would result in the delay or loss of the benefits of research.” The data reported by Getz shows that Yarborough’s prediction
has materialized, suggesting that issues of trust have not been addressed adequately to date.

Transparency

Transparency is one mechanism viewed as helping to build or restore trust in clinical trials. Beat E. Widler reviewed the growth in emphasis on transparency over the past 10 years, and noted that the push for greater transparency has several drivers. One is ethical, arising out of a concern that researchers were selectively publishing positive findings. Clinical trials registries were conceived as a way to reveal all aspects of a research protocol. Selective publication would thus be reduced as researchers would know that the incomplete data could be compared against the complete protocol. In addition, registries would provide information about relevant studies to people seeking to participate in research. People with serious illnesses had complained about difficulties accessing information about studies. This led to the registry, www.clinicaltrials.gov, going live in 2000. Such registries should also reduce duplication of clinical trials as researchers and funders will be aware of ongoing trials prior to commencing their own.

Another concern noted by Widler was the lack of transparency regarding the role of pharmaceutical companies and key opinion leaders in the conduct of clinical trials. The International Committee of Medical Journal Editors (ICMJE) published new guidelines in 2001 on the requirements for all authors listed on publications to have meaningful involvement in the study. In 2004, the attorney general of New York accused Glaxo SmithKline of withholding important clinical data about the effects of its antidepressant paroxetine on children. The company had reported the data to FDA, but had not made it publicly available. The ensuing settlement led to the data being placed on a public web site, and contributed to further transparency of all clinical data. This has led to other clinical trials registries that make data about planned and ongoing clinical trials highly accessible. ICMJE now requires that clinical trials, including Phase 1 trials, be registered in the World Health Organization’s registry as a criterion for publication in its 12 high-impact journals.

The inclusion of Phase 1 trials in the ICMJE require-ment arose in the aftermath of the TeGenero incident. The healthy volunteers in this 2006 Phase 1 trial suffered serious adverse effects after receiving an experimental superagonist monoclonal antibody. Widler used this incident to discuss some of the limitations of transparency. He concluded that had the TeGenero trial been included in a registry, it is highly unlikely the tragedy would have been avoided or lessened. The problem is that prior to the trial, the evidence of increased risk to participants was buried within masses of data, making it “doubtful that the needle would have been found in the haystack of unstructured summaries of results from so many trials on so many different investigational products.” Transparency cannot replace the importance of professional and ethical responsibilities on the part of researchers toward current and future participants.

If patient participation is a reliable measure of trust, clinical trials registries have not increased trust. Widler cited some limited data on trends in patient recruitment with the introduction of a registry. Little change has been noted. In addition, some registries offer little time for participants to enroll in trials. Widler concluded that a registry of patients seeking to volunteer for trials would be more beneficial for patients. Registries can also be expensive and time-consuming to build and maintain. New databases are being developed for various regions and countries, which duplicate many of the efforts. Widler would prefer an approach where one central registry is used, and suggested that this should be the one at the National Institutes of Health (NIH), since it is already the largest in the world.

Widler noted that “there is an assumption by many that greater transparency is inherently a good idea for society.” However, while O’Neill values transparency, she is skeptical about its potential to improve trust. She notes that deception and misinformation are the enemies of trust, not secrecy and lack of transparency. Those issues are not necessarily confronted by transparency, and will be examined later in this article.

Public outreach

One of the problems underlying lack of participation in clinical research is believed to be a lack of informa-
Fewer than 5% of Americans know where to find information about clinical trials and almost two-thirds were unable to name a single institution or organization conducting medical research. Almost every American adult questioned in one poll reported that they did not know how to access clinical studies or evaluate which might be appropriate for them.

In response, various resources have been developed to provide information on clinical trials. Most registries have web sites to provide information on specific trials. However, other information on clinical research may not be so readily available. For example, people with serious illnesses who are looking for experimental treatments may not be aware of the implications of random assignment. Other resources that provide general education about the nature of clinical research are now available from various federal agencies.

Diane Simmons gave an overview of steps taken by CISCRP to promote public trust by increasing awareness of how clinical research improves public health. In collaboration with a number of other stakeholders, CISCRP has developed brochures, DVDs, and newsletters. A more user-friendly portal for finding clinical trials has been released, along with other web-based materials. Collaboration with patient advocacy groups and other community organizations is being actively pursued.

CISCRP also has developed a public service campaign called “Medical Heroes,” designed “to educate and win over the public about the importance of clinical research participation.” The campaign includes a series of advertisements, including a 1-minute video available on the Internet. The materials present ordinary people contributing to the development of cures and thus advancing medical science through their participation. This message contrasts with the public perception noted in Getz’s article, where polls found that participants were commonly seen as selfish or risk-takers.

According to marketing research conducted when the Medical Heroes campaign was tested, recruitment increased significantly. Twelve U.S. markets ran traditional recruitment campaigns while six others used the Medical Heroes program in addition to a typical campaign. The latter had a 38% increase in patient enrollment over the control group. A repeat run of the campaign led to a further doubling in enrollment.

CISCRP plans to release the campaign nationwide so that it reaches about 120 million people each quarter.

Along similar lines, U.S. Representative Rick Boucher (D-VA) wrote about a resolution introduced into the House of Representatives in 2007. The purpose is to honor and recognize the contributions made by clinical research participants. The broader aim of his scheme is to increase public awareness of the contributions made by participants and the opportunities available for others to enroll. The bill was referred to the House Committee on Energy and Commerce in 2007 but no further action was taken on it.

Public outreach on clinical research is already much more common in the United States compared to Europe. More than two-thirds of Americans are exposed to promotional material about clinical trials through various media, whereas fewer than 10% of Europeans receive such material. Yet in spite of this, as mentioned earlier, participation rates in the United States are decreasing steadily. While public education campaigns can address information deficits, they may not be sufficient to address issues of trust.

Underlying such approaches is an assumption that “education and outreach are the keys to increasing trust and understanding.” However, this assumes that much of the problem lies with the public lacking information or being misinformed about clinical research. This approach is very similar to the “public deficit model” adopted earlier to address concerns about public mistrust of science. This model has been criticized as inadequate, on its own, to address issues of trust. While information is important in recruiting participants, it is not sufficient to address issues of trust.

Research on the public mistrust of science provides important insights here. The public deficit model has been criticized for focusing primarily on “incompetent publics, irresponsible and misinforming media, and non-governmental organizations.” What is avoided is careful reflection on the role of institutional science itself in the loss of trust. This self-critical analysis is essential if systemwide problems are to be identified and corrected. Other industries that have successfully addressed crises of public mistrust have found this process essential, if painful and difficult. When conducted successfully, one industry leader
noted that “arrogance gave way to humility and responsiveness,” which ultimately led to restoration of trust. This leads to the role researchers themselves play in building trust.

**Role of researchers**

Others have pointed out that clinical researchers can learn much from other enterprises (like the nuclear power industry and airlines) that have faced crises in public trust. Getz also looked at what clinical researchers can learn from the recent history of organ donation in the United States. In the 1980s, public perception of organ donation and trust in its procedures was on the wane. This arose after a number of high-profile errors caused suffering and deaths, a shortage of organs existed, and organs were being distributed inequitably. Due to a number of initiatives, the number of people donating organs increased two-and-a-half fold between 1988 and 2008.

Getz reviewed some of the initiatives taken to increase organ donation. These included legislators, foundations, and professionals working together to promote organ donation as an altruistic act. Public education and outreach was pursued via public service announcements, similar in many ways to Medical Heroes. Opinion polls from the late 1970s and early 1980s reveal similarities between organ donation and clinical research. Then, 90% of Americans believed organ donation was a good thing, but fewer than 40% stated they would donate an organ. This compares with the apparent contradictions in the statistics cited earlier on current opinions about clinical research. However, it is not clear that the problem is one of trust rather than motivation to donate one’s body and time for the good of others. Getz noted how many of the initiatives begun by CISCRP have been modeled on the approaches taken with organ donation.

Joy Frestedt discussed the role and impact of the principal investigator in clinical research. Certification programs for researchers are being developed, though currently are not required. Certification is available as a certified physician investigator or as a certified clinical trial investigator for non-physicians. Through certification, investigators can receive the necessary training in conducting research competently and appropriately. Participants can therefore have some confidence in the background competencies of researchers.

The table below lists those factors that Frestedt anecdotally collected while conducting several trials. This list reveals that many of the important elements are not skills, but character qualities. The importance of the researchers’ character and attitude was rarely addressed. Yet most of the problems that are cited as leading to loss of trust originate in moral failings: lying, fabricating data, greed, and placing personal interests above those of patients and the public. As Thomas L. Adams mentioned in his commentary, an important element of restoring trust is helping develop researchers who are known for being “as good as their word.” He noted that patients are probably not concerned with measuring trust, but with finding ways to participate in trials conducted by trustworthy researchers. Such character development is more challenging to foster and nurture, and far exceeds simple compliance with regulations.

**The views of participants**

Lisa Kaeser and Yvonne T. Maddox reviewed the NIH’s Public Trust Initiative. Begun in 2004, its mission is to help the public understand and have confidence in the clinical research conducted at and funded by the NIH. The initiative has identified various programs

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<td>• A caring principal investigator and staff</td>
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<td>• A welcome feeling</td>
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<td>• Immediate answers to questions</td>
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<td>• Discussion about the background of the trial, including interesting results from prior research</td>
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<td>• Valuable information sharing</td>
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<td>• Interesting discussions about the successes (or difficulties) in the trial</td>
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<td>• A specific interest by the staff in the person participating in the trial</td>
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<td>• A convenient location</td>
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<td>• Appropriate reimbursement for expenses</td>
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<td>• Great equipment/lab information</td>
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<td>• Availability of research treatment</td>
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<td>• A feeling by subjects that they are getting the best available medical care (even though clinical research differs from medical care)</td>
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already occurring in individual institutes. Several community-based events have been held to learn from participants and community leaders about why people participate or do not participate in clinical research. The NIH is now making small grants available for innovative projects designed to improve public understanding of research, promote collaboration between researchers and the community, and increase the effectiveness of relevant interventions.

One of the very interesting and informative perspectives comes from research participants. Jo-Ann C. Sebastiano was a researcher in the pharmaceutical industry who became a research participant after being diagnosed with cancer. She acknowledged that she had formerly “felt distant from” research participants “in the sense that I was looking at their data and not acknowledging the human beings behind that data.” She formerly viewed researchers as “tools” for completing research projects, but after becoming a participant she saw them as “experts” and “true patient advocates.” Overall, her faith in clinical research as a process that ensures patients “are treated ethically and holistically” was strengthened by becoming a participant. Even when she declined to continue into the second phase of the trial she continued to be treated with respect.

Cynthia M. Sinsel was trained as a biologist and became involved in clinical research as a monitor. She became an advocate for the vulnerable who enrolled as participants. Then she too was diagnosed with cancer, and the researcher became a patient and research participant. Her article described in detail her journey through clinical research. Her experience was very positive as she was comforted by the care and humanity of the researchers. The altruism of participating in research helped her with the experience of getting cancer. “Giving of myself felt good and transformed catastrophe into gift.”

Sinsel’s altruistic motives for becoming a research participant are widely lauded, but others enroll for more pragmatic reasons. “Professional volunteers” who earn an income through participating in clinical research raise additional ethical issues. Mather described an interview with one such professional volunteer and provided a less frequently heard perspective on clinical research. Sarah, a pseudonym, was a heroin addict who enrolled in trials to support her habit. Raised in a good home, she became addicted after graduating from college. She learned of clinical trials through a free alternative newspaper and word of mouth on the streets.

The interview provided fascinating, if disturbing, insights into addicts enrolling in trials. Sarah remembers little about what she was told or what she did. All that was on her mind was how much she would get paid. Her memory of the informed consent process was one of researchers summarizing information and getting her to sign many forms. Sarah cannot remember if she was involved in more than one study at the same time, but did not know this was a problem. In one study, participants were required to test positive for cocaine and heroin before enrolling. Sarah had only been taking heroin at the time and asked for her payment before participating so she could go away, get some cocaine, and return eligible for the study.

This article, while disturbing, makes an important contribution to the literature. It raises several ethical concerns about the reality of conducting research, even research that has received “ethical approval.” While precluding people like Sarah from clinical trials might seem to be one solution, she noted that the check-ups she received before studies were her only form of medical care at the time. Ethical dilemmas of this sort will not be addressed by regulatory compliance, but rely on the moral character of the researchers involved.

Pamela Wolfe provided one more insightful article into clinical research from the participant’s perspective. Having been diagnosed with cancer, her scientific and analytic background led her to investigate her options thoroughly. Her account provided an inside view into decision-making where important life goals are weighed and balanced along with the usual considerations of risks and benefits. The account revealed the importance of language and careful listening to patients’ concerns. For Wolfe, statistical information was important, but not forthcoming from some of those informing her about her research options. The lack of background preparation and attentiveness to her concerns led to frustration and anger, and this from a participant with a career in clinical research. Wolfe and her fiancée felt they were viewed as stupid for asking certain questions and crazy for considering one of the options. “We began to question the validi-
ty of the information we were given and the expertise of the practice. In addition, we felt we were being pressured into joining a trial.25

With disappointment, Wolfe decided not to participate in the trial. She remains committed to the value of research and would consider it an honor to be a research participant. Ultimately, the problem was that Wolfe felt she was not regarded as an individual. Instead she was “patient #427 in a Phase 3 study.”25 The other problem was that she felt pressured to enroll, as if a quota needed to be met. Instead, what she wanted was to be shown compassion and concern.

Such testimony shows the limitations with public information about clinical research. Wolfe was well aware of ongoing trials and how to access information. Her own education allowed her to process and evaluate her options. Yet her experience was negative, due primarily to the interpersonal dynamics of her interactions with one of the research team members. From Wolfe’s article, it would seem that the team member did not break any regulations or ethical codes. Yet her interactions did much to compromise Wolfe’s trust in the research enterprise. This points, once again, to the importance of addressing character issues and attitudes, not just information and regulations.

**Ethical development**

Central to building trust is ensuring that clinical research is conducted ethically.1 The Tuskegee Syphilis Study was one high-profile, shameful research project that continues to generate mistrust among African Americans for clinical research.26 One response to the scandal was to provide NIH funding to develop bioethics education for clinical researchers. A number of training programs have been developed, yet their impact remains relatively unknown. A review of one such program recently found that while participants found the course beneficial, their scores on tests of ethical problem-solving skills remained the same or decreased.27 Such lack of impact of ethics training programs is not unique to research settings, but a general problem with the way ethics is currently taught.28,29

A general strategic plan for addressing ethical issues in clinical research does not exist, even at the NIH.30 Salerno has claimed that there exists “a lack of appreciation for the centrality of bioethics across the biomedical research enterprise nationally,” which is an important contributor to public mistrust of clinical research.26 Part of Salerno’s concern arises because she believes bioethics programs have not focused on “fundamental matters of attitude and ethical questioning that should infuse and inform every aspect of biomedical research.”26

A consensus opinion has existed in medical ethics training that it should not be expected to “create sound moral character,” although this assumption has been challenged recently.31 If trust is based on how people treat one another and interact with one another, ethics and moral character are central. The researcher who gave Sarah money to get cocaine that would make her eligible for the study acted ethically. The researcher who failed to listen carefully to Wolfe failed to live up to the ethical standards revealed by those who interacted with Sinsel. Those are the issues that need to be addressed if trust is to be restored.

**Conclusion**

“There is a unique but closing window of opportunity for stakeholders in the clinical research enterprise to build collectively on this foundation in order to restore public confidence and trust.”6 Many practical initiatives may play a role in helping to restore public trust. However, some may lead to increased enrollment without necessary restoring general trust in research. The assumption that enrollment levels and public trust can be directly connected needs to be examined thoroughly, especially given the evidence that clinical research remains highly valued by the general public.

The general assumption of the public deficit model is also problematic. It tends to instrumentalize public trust, suggesting it can be restored through programs and initiatives. Part of the problem is that it is inappropriate to expect others to trust us and make that the goal of our actions. “The only thing which one can expect to control, and to take responsibility for, is one’s own trustworthiness.”17 This requires a willingness to look at one’s own contribution to the breakdown of trust. “We have met the enemy and he is us.”4 Building relationships with the community and identifying common values and goals are crucial to
trust. The idea of “leaving something behind” in the community is important to participants. In learning from other industries that have restored public trust, relationships and character issues were central. Many of the lessons learned centered on leadership, which helped people learn to be humble, honest, open about fears and the unknown, and responsive. A code of silence and a shame and blame culture had to be replaced with one in which the root causes of problems were sought.

In setting out to restore public trust, there is a danger in simply assuming that the clinical research enterprise is trustworthy and that the public just needs to be shown why. Trust must be restored and rebuilt, whether in public or in private. “Trustworthiness is an accomplishment, not a pronouncement. If it exists, it is embodied in the daily actions of the institution and its members.” Reflection on one’s own character qualities and actions is necessary. Then the one seeking trust must humbly go to the other and patiently wait while demonstrating they are trustworthy.

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