



## INSTITUTE FOR ALTERNATIVE FUTURES

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Finally, we are very grateful for the many ideas and insights in this report that were generated by the workshop participants named in the Appendix. The report presents an exploration based upon diverse views of the participants and does not attempt to reflect a consensus. Therefore, it is possible for the participants, as well as other readers, to find

areas of agreement and difference in this report. IAF solely is responsible for the opinions presented and any inaccuracies in this document.

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## EXECUTIVE SUMMARY

The *Clinical Development 2005 Report* describes four strategies to significantly reduce the time and cost involved in the research and development of new pharmaceutical or biotechnology agents. The strategies identified in this report could cut the cost of developing new therapies, which have been reported to now reach as high as \$500 million or more for some new pharmaceuticals. More significantly, these strategies may cut development times by half. An added benefit is that these designs could also increase the quality and quantity of information that reaches those making medical decisions. The strategies in this report introduce a paradigm for a 21<sup>st</sup> century system of clinical development to improve health.

### Section I

**Clinical Epidemiology/Human Genetic Factors** describes one of the four areas through which new knowledge can contribute to clinical development. Clinical epidemiology supplies a macro view of populations that, combined with the new micro view of individuals developing from the map of the human genome, can supply a new paradigm for clinical development. New approaches can use longitudinal data in electronic medical records, and include information about genetic markers. The markers will reveal patterns of individual responses to medicines along with data based on population norms. These patterns will place the individual, rather than the disease or indication, at the center of research. This shift can make retrospective studies more central, opening clinical development to both a change of paradigm and a receptivity to new research methods.

## **Section II**

**Computer Simulation** is among the most exciting of the new methods because it holds the potential to generate more learning per dollar from data collected in clinical development. Powerful supercomputers and software tools can create models of human biology that predict the human response to medicines. These results can then be tied to real clinical data in fast feedback loops. As the models improve, the need for confirmatory data diminishes. Computer simulations can be used with the goal of reducing the time for each of the clinical phases and reducing the number of people needed to test experimental compounds. In time, it may be possible to approve new therapies using computer simulations and a single, confirmatory clinical trial.

## **Section III**

**Outcomes Studies** present another area for new knowledge, including the value to society of the billions of dollars spent in clinical development. The growing collaboration across disciplines in outcomes research can use advancing technologies and expanding new data bases to answer more complex questions. By adding layers of contextual information, researchers can look beyond the safety, efficacy and quality of products to larger questions that society needs answered, such as whether the costs of medical products are justified by their benefits. Beyond the limits of current cost-effectiveness studies, collaborative research can measure the value of various contributions to health care, as well as health itself. The results should help focus research and development towards those health areas with the potential for significant health improvements and societal savings.



## Section IV

**Community-Based Studies** holds the promise that new knowledge from research and development can be better integrated into the real world of medical practice and daily life. Massive amounts of data will be flowing over fiber-optic cables that connect healthcare systems and, increasingly, homes and communities. Clinical development can take advantage of these enhanced data sources, potentially creating a new approach that places each individual into multiple, “virtual” cohort databases. Pilot projects now emerging and incorporating electronic medical records provide an early source for relevant data. The statistics drawn from individual records can create “enhanced cohort data” if the public agrees to participate. The potential benefits of this participation include better research and development as well as smarter markets and an improved healthcare delivery system.

## Section V

**An Emerging Paradigm** that crosses all four of the areas explored in this report shows progress coming along three dimensions. The dimension of technology moves an essentially paper-based system to electronic data exchanges and computer modeling. Another dimension uses knowledge of human genetics to move from “massified” knowledge about average responses of populations to medicines toward customized therapy for each person. The third dimension moves from the current “blinded” state used to create objective information to “knowledge-based” development that integrates subjective responses of patients. This knowledge base will encompass not only clinical data, but other forms of information about healing in all its dimensions.

## Section VI

This report concludes by proposing steps to move the clinical development system into this new paradigm. The section entitled **Next Steps** describes a proposal to apply this emerging paradigm to make clinical development more helpful to the practice of medicine as it takes place in the real world—in both conventional and alternative forms. A series of steps is proposed to gather support from leaders in the private, public and academic sectors who want to commit to progress. One step is to set ambitious goals to move clinical development into the future. Another step is to develop a forum where continued progress in clinical development is encouraged and guided. The Institute for Alternative Futures proposes to work with others ready to take these steps. This report invites readers to respond with ideas and comments that can help create a clinical development system for the early 21<sup>st</sup> century.

## INTRODUCTION

Clinical Development 2005 is a collaboration of over 30 experts to examine a thesis and propose a process so that clinical development of human health care products and services can be significantly improved. This report summarizes a one day invitational workshop on October 23, 1996, at Georgetown University (Washington, DC, USA), to identify the trends and possible breakthrough innovations that may contribute to clinical development improvements.

The readers of this report are invited to engage the authors and workshop participants in a dialogue to continue to explore this thesis.

### *PROJECT THESIS*

The Institute for Alternative Futures (IAF), the Georgetown University Center for Drug Development and IMS America began the Clinical Development 2005 dialogue by posing the following hypothetical question to over 50 recognized clinical developers and researchers:

“If we could construct a graph showing 'learning per clinical research dollar' beginning with the year 1962 and ending today, what would be the shape of the curve?”

**Most of the queried experts said the curve is now flat, or worse, sloping downward!**

These responses led the principal organizations to convene an invitational workshop to discuss a working premise and proposal:

***Premise:***

***The current status of clinical development has understandably grown out of an “industrial model” of product development, surrounded by centralized policies and focused on standardized risk reduction. The current approach shows many signs of social, technological and economic obsolescence.***

***Proposal:***

***By taking a “systems view from the future” we can recognize the emergence of a totally integrated, continuously evolving system which embodies the combined principles and processes of “healing”, “learning” and “creating”. From this view, more highly-leveraged strategies for change and more recognizable “progress thresholds” may be identified and fully utilized.***

The workshop brought together experts from many complementary fields to share their thoughts on the potential for improving clinical development. Included were successful medical researchers, expert clinical managers, former government officials, and business leaders from medical, health, information technology and engineering industries. The workshop participants are listed in the Appendix.

The workshop was organized to examine four topics identified as potential sources of significant improvement. The topics were:

- 1) **Clinical Epidemiology & Human Genetic Factors;**
- 2) **Computer Simulation;**

- 3) **Outcomes Research; and**
- 4) **Community-Based Studies.**

The workshop participants were asked to join a small group to discuss one of these specific topics. Each small group met twice and reported to the entire workshop. Each small group performed two exercises. The first exercise was to identify the technological or intellectual trends affecting the topic and then to identify the leading and lagging practices in that topical field. The second small group exercise was to suggest strategies for accelerating change within the topical field or throughout clinical development. All small groups prepared and made reports to the full workshop, which concluded with an open-ended discussion to examine what had occurred.

**The major insight from the workshop is that tremendous improvements can and should be made in the years ahead.**

#### *WHY CLINICAL DEVELOPMENT?*

When IAF began talking about "clinical trials 2005," thoughtful critics told us to change the focus to **Clinical Development 2005**. The name change is important because it reflects a change of focus away from human clinical trial design to the whole process of developing human health care products and services.

Clinical Development 2005 challenges leading health care developers to re-examine today's "gold standard" of double-blind, placebo-based clinical trials, in light of possible improvements throughout the clinical development process. The report's authors and the workshop participants all agree that clinical trials have served the public and that their

continued improvement is essential. Health care providers and innovative companies have learned important information through clinical trials for over three decades. The “blinded” studies have provided an objective view of experimental compounds and a degree of rigor that has created confidence in medicines.

Clinical trials should not be abandoned. Nevertheless, as we approach the end of the 20<sup>th</sup> century, we should recognize that celebrated designs created almost 50 years ago may need to be improved to take advantage of new biological knowledge and information technology. By 2005 the structure of the medicines approval process could be far different if we use these emerging tools and new knowledge to their fullest potential. The clinical trial may well become less central to learning about medicines. By taking a fresh view of the entire system for developing new medicines and the knowledge to best use them, the authors and workshop participants hope that clinical trials will be used optimally with other methods.

### *PROJECT NEXT STEPS*

This project is an invitation to “think outside the box”--to take risks by questioning established practices. People most comfortable with the status quo may find the whole effort controversial and disturbing. Others will embrace the hope for progress.

IAF agreed to produce this report as the first step to move us toward innovation in clinical development. We invite readers of this report to take notes, identify opportunities for progress that need more attention, and share resulting insights with IAF.

IAF expects to take further steps based upon feedback from participants and readers. One step is to convene more people who want to contribute the intellect, creativity and drive needed to make the striking improvements in the development of medicine that this report points toward. Many other steps need to be taken between now and 2005, and we invite our readers to join by committing to future steps.

### *STRUCTURE OF REPORT*

This report's structure is based upon the workshop agenda. Summaries from each of the four topical small groups are presented in separate sections. The workshop's open discussion is summarized in two sections: An Emerging Paradigm and Next Steps. An appendix listing the workshop participants is included.

IAF, the Georgetown Center for Drug Development and IMS America invite you to join this dialogue and make healing, learning and creating a reality by the year 2005.

## Section I

### CLINICAL EPIDEMIOLOGY/HUMAN GENETIC FACTORS

The mapping of the human genome will revolutionize clinical development. Linking clinical epidemiology to the understanding of human genetic factors will create a dynamic learning cycle between the macro-view and the micro-view. The macro view of epidemiology centers on what we can learn about health, disease and medicines by studying populations. The micro-view that human genomics will bring is to see individuals through the lens of genetic processes. The combination of views can create the ability to identify sub-populations that have different responses to medicines.

Classical studies have considered the percentage of a population showing a specific effect after taking an experimental medicine, along with the percentage not having an effect, to arrive at a conclusion. The conclusion may be more or less true for different individuals, and to date that has been accepted as good enough. However, the combination of clinical epidemiology and molecular genetics could provide a new approach for learning about medicines in the context of both populations and individuals. “Good enough” could become much better.

The new approach arises from the understanding that providers and individuals in society can gain about the role of therapeutics. From a longitudinal view of individuals and populations, therapeutics can be seen in the context of whole lives. Rather than isolating single symptoms that respond to a given therapy, the goal can be to understand the multiple impacts that treatments will have on populations and different sub-groups. New



models that can integrate genetics, time and population-based information need to be developed.

There will likely be tradeoffs with the new models. The economic incentives for product development are likely to change with the advent of a longitudinal view of both populations and individuals. Preventive products can be expected to have a far more attractive economic position. Epidemiologic data that includes genetic markers to indicate potential for adverse effects would help refocus R&D. In the redefined model for R&D and economic success, a greater number of compounds will be available for groups containing a smaller number of individuals who most clearly benefit from the medicine.

The new model of clinical development could bring a need for individuals to have “genetic profile cards.”. Genetic information could identify whether an individual is a rapid or a slow assimilator of drugs, for example. This information could help improve therapy, but it also could be used for insurance exclusions or other forms of discrimination that go against important values. Ethical issues and privacy concerns will arise and will have to be addressed if we are going to create an optimum clinical development system. Already, information about cancer genes is difficult for individuals and health-care systems to assimilate and use. This genetic information is only the beginning. Further advances will come with more ethical dilemmas that need to be addressed to gain the benefits of new knowledge.

The group discussing clinical epidemiology & human genetic factors was asked to identify “lagging” and “leading” edges within this field, and to present some strategies for improvement.



## LAGGING EDGE

- Patent law is a lagging edge that will present problems as new genes are discovered. The ownership of information that contributes to innovation will become more contentious as the value grows, particularly when it leads to prevention.
- Public discussion of ethical issues is falling behind scientific progress. The problems that will be created from early use of partial information may define the public response if people are not engaged in an understanding of the benefits of the knowledge we will gain. We may realize benefits of scientific knowledge much later than we would want because of the failure to engage the public in a full discussion of risks and benefits.
- Longitudinal studies are infrequently performed. Few electronic databases contain more than five years of experience, and the research programs with more years of experience either have too few subjects or are not accessible to researchers. While low funding of longitudinal studies generally explains the lag, the declining cost of data collection is beginning to overcome the economic barrier.
- We have chaotic standards of evidence that reflect legitimate differences in view. Statistical standards can conflict with standards that individuals might choose, and yet both are valid within different value schemes. The desire for a single standard to which all cultures must conform continues to be frustrated. The inability to recognize how cultural and personality differences create different views of standards creates an ongoing lag factor.



## LEADING EDGE

- Blood banks and cell banks are a powerful source of genetic data that have the potential for helping identify sub-populations that vary by drug response. The need for molecular-marker databases could make such existing databases valuable.
- The better understanding of molecular biology joins combinatorial chemistry and computer assisted design (CAD) technology to form a better understanding of medicines in human systems.
- Diagnostic systems for genetic markers are advancing rapidly. Micro-chip technology now provides for fast and inexpensive assays. Future advances should lead to earlier diagnostics and better integration with both therapeutic and prevention strategies.
- Enhanced cohort data is increasing the ability to learn from other data-sources including non-randomized trials. The striking increase in the amount of information collected and stored at lower costs promises to provide more knowledge if new software tools continue to develop.
- Electronic medical records are providing access to millions of individuals' clinical experiences. The resulting flood of data is giving researchers a wealth of variables to correlate. As these correlations reveal patterns, the ability to learn from retrospective studies should grow to provide an economically attractive contribution to clinical development.

## STRATEGIES FOR PROGRESS

*Define the new “paradigm.”* The revolutionary clinical development paradigm coming from the map of the human genome places the patient at the center of research, rather than the disease or indication. Now we need to define how this new paradigm can change the research process. There will be a large number of questions to answer about the advantages and disadvantages of change. Methodologies will be needed in order to integrate new genetic knowledge with existing clinical data. New economic and business models will be needed to address the question of cost-effectiveness. By defining the new paradigm for clinical development, we can provide a framework for individuals working within the system to understand how they are advancing science in the public interest.

*Create a linkage between disease statistics and genetic markers.* Every genetic discovery will provide us with pieces and clues to solving many medical puzzles. We will have to pay close attention to many of these clues in order to make the connection between existing disease knowledge and emerging understanding of genetic predispositions. The linkages will be important for forming a system for genetic profiling of population subgroups and individuals.

*Educate the public.* One of the biggest challenges confronting the scientific community is educating the public about new genetic discoveries. Genetic knowledge will perplex a large portion of the population. Confusion over the knowledge of disease and genetic markers will create a difficult barrier for regulatory change that will be needed to advance clinical development. Scientific

illiteracy can be addressed through an education campaign to explain to the general public the intricacies of human genetics. We must create educated consumers to take advantage of scientific knowledge.

*Realize the economic value of going from treatment to prevention.* Our current health care system spends millions of dollars in treating diseases and their symptoms. This has been standard practice because of our limited disease knowledge. Assuming that molecular genetics will provide us with new knowledge about disease, we will then need the economic evidence that can help shift spending practices to fund prevention over treatment.

*Expand the focus of epidemiology.* Our focus on epidemiology should consider all the factors in the system which contribute to health, not just illnesses. As systems center care on individuals and develop medicines that contribute to their health, there will be a growing need to understand the factors and patterns that contribute to healthy lives. These factors will include non-medical as well as care-giving determinants that are relatively unstudied to date.

The people who focused on Clinical Epidemiology/Human Genetic Factors and led the group discussion included:

Judith Jones

Robert Desjardins

Robert Merold

Gio Gutierrez

## Section II

## COMPUTER SIMULATION

Advances in computer simulation can contribute significantly to the process of clinical development. Computer simulations can combine data with insight, forming a feedback loop that gathers more information and confirms the insights at a lower cost than more purely empirical processes. Feedback loops that abstract more information per bit of data promise to change the economics of clinical development and open up opportunities for new methods.

**News Flash & Forecast**

*The Washington Post*, December 17, 1996, A-1: “Researchers said yesterday they have designed a supercomputer that can handle a staggering 1 trillion mathematical operations per second....and will be able to operate at 1.4 teraflops.... The Intel supercomputer is the first step in a 10-year government plan to develop a 100 teraflop computer....3 teraflop machines.... are expected to be in operation by early 1999....

More powerful computers offer the opportunity for clinical development to develop simulations based upon existing knowledge before an experimental compound is even given to a human subject. Responses predicted by the simulation can then be compared with the human response of a test subject. In effect, the simulation creates a model for what is known while the human provides feedback on the model. The feedback tests what is known and reveals clues about what is unknown.

An expert in high-performance computing, Dr. Lucian Russell, characterizes the opportunity that supercomputers will create this way: “The projected increases in computing power allow us to think about simulating the cumulative effect of the interactions of drugs with the human body over a period of years.”

Critics argue that today the larger number of test subjects in poorly designed clinical trials merely compounds ignorance when the costly results never succeed in demonstrating safety or efficacy. Computer simulations could limit this problem, but could also move clinical development beyond providing answers to questions that are already answered by today’s clinical trials.

In the future it is even conceivable that computer models will advance to the point where medicines will be developed almost entirely by simulation, with only a single, confirmatory clinical trial before approval. This may appear to be a bold prediction given progress to date, but technological advances in computer hardware and software will come at a faster rate than ever before. Experience may therefore be a poor guide for judging potential progress in computer simulations.

Computer simulation can help manipulate data to gain insights into a larger number of variables that relate to the effect of medicine. The insight gathered from each development process can also be used to improve future trials. One goal of simulations should be to use the information that is gathered from human trials to discover ways to

reduce time within each of the clinical trial phases, and in some cases eliminate the need to test on humans.

Such a dramatic reduction in the need for human trials may appear unrealistic in today's world, but systems can change rapidly when new technologies are introduced. The 100 teraflop supercomputer described above, for example, could help scientists move towards new designs for the current drug development process. Early experience in computer simulation needs to be closely studied to find where future opportunities with more powerful technologies may exist. The group discussion focused on advantages and shortcomings currently existing within computer simulation of clinical research and strategies for improvement.

The group identified “lagging” and “leading” edges within computer simulations and present strategies that would contribute to improving and advancing the clinical development process.

### LAGGING EDGE

- We are only beginning to develop models of endpoints and clinical outcome observations. Our ability to model outcomes does not yet exist. Our disease models simply are not here yet because we cannot model what we do not know. Computer capacity is available, but the software tools are just emerging.

- We currently lack validation for computer modeling. The receptivity from the culture does not yet exist. This includes both regulators and industry. We lack the integration of technical backgrounds from different disciplines. For example what can we learn from aerospace?
- We have yet to incorporate genetic knowledge in clinical development.
- The body is a black box and even past the gene map, we will not know enough to design therapeutics.
- A comprehensive, futuristic vision of how computer simulation can be used is still missing.

#### LEADING EDGE

- We have the access and opportunity to learn from models that other industries have created.
- Rapid information retrieval capabilities are available.
- The ability for auto sequencing has grown.
- Enhanced data capturing techniques for use with Electronic Medical Records (EMR) is at hand.
- Artificial intelligence software is available for simulations. There has not been user-friendly software until now, but that threshold is crossed.
- Simulations can create emerging standards for methodology that can advance beyond simple repetition.
- Health status measures are developing for populations and individuals.

- Customized studies of individual decision making can be integrated into clinical trials to refine the ability to gain compliance from subjects, as well as to identify significant factors affecting cost effectiveness.

Having identified the “lagging edge” and “leading edge” for simulations in clinical development, the group also explored different strategies that can promote progress.

### STRATEGIES FOR PROGRESS

*Begin with basic science.* We have access to a substantial amount of data about disease states, patient records and clinical data from a variety of different sources. Integrating this information and making it accessible can help us create models. If we can provide a richer and more substantial source of information we can improve our learning and outcomes.

*Improve clinical development efficiency.* Efficiency has always been an issue in maintaining and improving any system. It is just as crucial in clinical development. Protocols for the clinical development process must be created, implemented and evaluated. It will also be important to ensure remote entry and access to information. With data accessed from anywhere at any time, the processing time can be shortened. With this enhanced data access, mechanisms will be needed to deal with data management. The data management system should address issues of access, accuracy, privacy and efficiency.



*Present a validation for simulation.* The process of computer simulation is at an early stage of development. Those who are pioneering in this field should illustrate the advantages and benefits of computer simulating. The general public will have to be informed and educated before industry and regulators will be able to institute change. Perhaps publishing reports, articles or employing the media to report the developments of simulation would convey its importance to the general public.

*Get FDA to lead in simulation.* This would be a powerful leveraging strategy that would position simulation as a new mechanism in clinical development. In order to advance this strategy there are other elements to consider. Before we can get FDA to lead in simulation we must ensure that they have the technology to do so. The agency would need to acquire adequate hardware and also a team of simulation specialists. Further strategies will be needed to ensure that the FDA can handle a new role as a simulation leader.

*Make basic information free and available.* The public can be educated by making information free and readily available to them. The public will also need to understand the information that is provided to them and the implications that it has on their lives. Technology is already playing a role in bringing information to the public. The Internet's growth and accessibility will have many implications in launching education campaigns for the public. Television and the Internet can combine to revolutionize the way we receive and retrieve information in the

future. The development of software agents to help people gain access to and learn from information may make this strategy more feasible in the years ahead.

*Create another “Manhattan Project” of sorts.* This idea comes from the conviction that a group of the best minds could create a significant step forward. If we could gather some of the best minds in clinical development and computer sciences and fund their work, the results could be striking. Who would fund and initiate such an effort? Among those who might take the lead are contract research organizations, venture capital firms, or a large company with deep pockets. For a major pharmaceutical company to take the lead and succeed, however, they would need to be willing to “break the mold” first.

*Ensure cost effectiveness.* Any strategies for developing computer simulation will have to account for questions about cost effectiveness. Questions include: What effect is it that we are trying to create? What outcomes or end-products will we deem as successful? Strategies will require an investment--whether it is financial investment or time investment, and we should consider the most effective way to allocate these resources before moving into simulation.

The many possibilities for using computer simulations in clinical development have yet to be fully clarified. Both possibility and feasibility needs to be assessed in the context of today’s technological capabilities and potentials we expect to have available. At this stage it is premature to weigh the potential contribution of computer simulations. We can

say only that this area appears to hold great promise that should be better understood and at least partially realized well before the year 2005.

The following people focused on Computer Simulations and led the group discussion:

Lucien Russell

John Beary

Carl Peck

Shawn Johnson

Daniel Wayne

Ana-Maria Zaugg

Mark Hovde

## Section III

### OUTCOMES STUDIES

Outcomes studies will contribute to and benefit from accelerated clinical development. The optimal contributions and results will follow after exploring challenges that outcomes research poses to current clinical development practices. These challenges are two fold: First, outcomes research by its nature proposes that current clinical development endpoints be expanded beyond the accepted and regulatory standards. Second, outcomes research, particularly cost-effectiveness research, challenges the medicines development process to demonstrate significant value for all health stakeholders.

In order to ensure that a process of “healing,” “learning” and “creating” leads to improved medical care and health, we must ensure that we are investing wisely. Innovative outcomes research can be the tool to protect this investment.

Outcomes research can make three strong contributions to clinical development. First, outcomes studies can elucidate health burdens and intervention benefits including:

- Epidemiology: the distribution and variance of health status across populations;
- Illness burdens: the economic and health burdens associated with disease.
- Intervention outcomes: economic and health costs, burdens and innovative services.

If these studies were accelerated in the near future, then researchers, medical professionals and patients would increase their health intelligence, improve their decision making and increase medical care efficiency. However, some clinical development of medicine still proceed without complete or near-complete information along these dimensions.

Therefore, some current clinical development projects are generating quality, safety and efficacy “results” that are missing important contextual information such as net impacts on health, the economy or estimated changes in total medical care and other expenses associated with the intervention. It should be noted that most new drug studies for important innovations now do include outcomes research.

Outcomes research’s second potential contribution to accelerated clinical development is that it simultaneously asks developers to incorporate both societal (e.g., economic) and patient concerns (e.g., pain and suffering) into their conceptual models and actual research. In the short term, these dimensions may increase the costs and complexity of clinical development, but already available and soon-to-be available technologies should reduce these expenses (see section on “technology implications” below). In the long-term, expanding clinical development’s end-points to include these dimensions will provide decision makers within industry, government, health care delivery, payer organizations and patients themselves with richer information and knowledge. This knowledge will promote more informed decision-making, helping to ensure that prices are valued appropriately and helping to send signals to the pharmaceutical industry to concentrate development on products with high value.

A third and more general contribution is that outcomes studies mirror the collaborative model for clinical development that the workshop attendees encouraged. Already, many outcomes studies are performed by multi-disciplinary research teams combining experts in medicine, economics, biostatistics, behavioral science, information technology and others. Furthermore, many outcome studies are inter-institutional including industry, academic and third-party consultants. It is foreseeable that most outcomes studies will become even more inter-institutional to further accelerate knowledge acquisition and the development of health interventions.

Three outside forces are generating benefits for outcomes research: Information technology, patient-centered care paradigms and genomics. Rapidly advancing information technologies are facilitating significant improvements in outcomes research. Information technology such as the electronic patient record and remote data entry are reducing the time to capture and analyze data. This topic is explored in more detail below.

Health care providers and patients are increasing their demands for more thorough information about health, illness and treatment. Quality, safety and efficacy are no longer adequate endpoints for patients and consumers juggling decisions about quality of life, adverse effects or costs. Both increased detail and expanded dimensions of information are being sought and provided. As a result, outcomes research is quickly becoming an element of clinical development and customer/patient relations.

Genomics is beginning to provide benefits to outcomes studies. As more is known about the nature of disease, then more can be understood about who will suffer, from what they will suffer and how they will suffer. In turn, outcomes studies can further illuminate how best to invest research funds. In the future, genetic information may drive the trend to tailored and customized services, treatments, medicines and devices. In this future, outcomes research will need to be redefined as the customization process will become the focus of evaluation, not the specific chemical entity.

The expert group began with a discussion of technological implications of current developments and identified lagging and leading research practices in outcomes studies practices. They also discussed strategies and goals to accelerate clinical development.

#### TECHNOLOGICAL IMPLICATIONS

The attending experts identified three technological trends that will have significant near-term impacts on outcomes studies: information technology, artificial intelligence/expert systems and clinical compliance technologies.

*Information Technology (IT):* Already, today's priority projects are taking advantage of data capture, transmission and management capabilities available through secure Intranets. Several information technology improvements should contribute further to outcomes studies' efficiency and productivity. Of these, two stand out: Data capture and transmission. Electronic data capture throughout health and medical care systems is recognized as a large potential source for quality improvements, cost reductions and clinical efficiency gains. The primary tool for data capture will be the electronic medical

record and its encounter form. New data capture technology may reduce the cost of clinical development. For example, home-based data-capture technologies may drive down the expense of research. Furthermore, electronic data capture of other information (e.g., medical care costs) will also speed up outcomes research. Electronic transmission of data also improves clinical development and outcomes studies' efficiency.

*Artificial Intelligence/Expert Systems (AI/ES):* The gathered experts briefly discussed the potential for AI/ES to contribute to outcomes studies. It was forecasted that artificial intelligence and expert systems will help design, manage and analyze clinical development and outcomes studies in the near future. Another possible use of AI/ES will be to develop, run and assess simulations. Neural nets, AI/ES that “learn” through the use of validation sub-routines, may be worthy of evaluation for use in clinical development and health services research.

*Clinical Compliance Technologies (CCT):* Researcher, provider and patient compliance have long been the bane of health product researchers, regulators and consumers. Examples of compliance failures include clinical researchers creating data entry short-cuts, providers “breaking blinded protocols,” and patients forgetting to keep appointments or take medicines. Compliance technologies can provide solutions to these and a wide variety of other compliance errors, thus improving the productivity and accuracy of clinical research and practice. CCTs are a set of technologies and processes that identify, avoid or resolve opportunities for both intentional and non-intentional compliance failures. Transdermal patches and portable intravenous pumps are patient compliance technologies, as are electronic, patient medical records that automatically prepare and transmit research data. CCTs generate two important questions for outcomes researchers.

First, CCTs must be evaluated for their effectiveness to create and maintain compliance behaviors. A second topic for outcomes research is to understand how CCTs may affect clinical development results. An associated question is whether CCTs have their own placebo effect, separate from the placebo effect associated with the product under investigation. CCTs solutions are expected to become key elements in clinical development protocols, and possibly in the products themselves.

A number of lagging edges were identified and acknowledged to perpetuate both low credibility and quality of outcomes studies. These areas were:

### LAGGING EDGE

- Few generally accepted standards for outcomes studies' models, protocols, indicators and measures;
- Clinical development projects that often engage outcomes researchers late in the development process. Much of a product's formulation, dosing, and potential indications have been decided before outcomes researchers can contribute to these discussions or examine what outcomes may be appropriate to study;
- Poor study designs: As the result of few generally accepted standards and the fact that they are selectively and belatedly involved in clinical development projects, many outcomes studies have poor designs;
- The lack of true cost data at the illness, medical care or societal level;
- Over-emphasis on economic costs and the under-emphasis on non-pecuniary costs and benefits: marketplace concerns have driven outcomes research to

focus on cost-effectiveness. Furthermore, the lack of true, total cost data has resulted in an over focus on economic costs (e.g., net expenditure and productivity changes associated with the studied intervention or product). Benefits are often less easily measured, particularly if they are not directly accounted for in economic terms. Most experts recognize the value of and the need for research into the non-economic benefits and burdens of health care services and products.

- Health care delivery systems (i.e., governmental, integrated or stand-alone) that do not have the ability to participate in clinical development or outcomes studies because they lack the infrastructure.
- “Snap-shot” data. A number of data failures were identified including protocols that ignore or eliminate longitudinal data from outside of the research period and protocols that do not collect data from various clinical or health settings.

Workshop participants identified two additional issues that contribute to lagging practices:

- Outcomes studies can increase the costs of medicines and device development. However, the experts noted that the cost/knowledge trade-off was significantly favorable in support of knowledge. The workshop participants suggested that the study costs could be controlled by engaging outcomes researchers early in the development process, employing AI/ES, simulations, designing studies carefully and using both IT and CCTs solutions.
- There is a fear that outcomes studies, particularly cost-effectiveness research, may become a new hurdle for medicines and device registration or

reimbursement. High research and development expenses and time commitments have made many research-based industries cautious about embarking upon research that is not required for product registration. However, government regulators and public and private payers are increasingly interested in cost-effectiveness and other outcomes studies to evaluate registration and reimbursement. Already, Australia and Canada have required CEA to be included in a new medicines request for pricing in national or provincial formulary approvals. The attending experts acknowledged this conflict, but generally believed that payer, provider and consumer demand for outcomes studies would generate these studies prior to significant new regulatory requirements.

### LEADING EDGE

The experts noted a number of leading practices including:

- Continued development of standard measures for health status, health and medical care costs and societal benefits;
- Increased cooperation among all stakeholders in health to explore and refine outcomes research;
- Accelerated information technology gains including the use of sophisticated data capture, transmission, management and analysis techniques and systems for global clinical and outcomes research;
- Renewed interest and use of AI/ES to drive medical, health and outcomes simulations that speed study design and implementation;
- Burgeoning departments everywhere.

## STRATEGIES FOR PROGRESS

*Involve outcomes researchers early in development.* Outcomes researchers can make significant and productive contributions early in the development process. Furthermore, early engagement can help reduce the costs of outcomes studies in later development stages.

*Create agreement on the meaning of value.* Because value (i.e., net benefits) is defined differently by all the stakeholders in health care systems and differing health care systems, experts should explore developing a consensus about what indicators and measures of value can be acceptable to all stakeholders.

*Look at total, long-term, societal costs.* Currently, many outcomes studies' analyses are retrospective; they often substitute price for cost and do not examine the societal and long-term costs and benefits of the intervention or health condition in question. The attending experts believed that the societal perspective is the most proper view for outcomes studies to take, though studies need to identify and examine the interests and net effects for all key stakeholders.

*Focus on "real" patients receiving care in "real" settings.* The experts highlighted the concern that most clinical development and outcomes research still occurs in academic settings with highly screened and limited patient selection criteria. Outcomes research needs to explore how these studies' results may differ

from likely and standard use of the interventions, preferably examining the interventions in actual clinical settings of care with less standard patient profiles.

*Focus and target the greatest potential for societal savings or health improvements.* Outcomes studies should identify where the greatest societal health benefits and burdens lay so that research and development entities can invest strategically.

*Increase health information technology investment, development and deployment.* If clinical and outcomes research is to expand outside the academic medical center and into managed care or neighborhood clinics, then these settings will have to be “wired” and their personnel trained and rewarded for technological proficiency. In the future, home or non-medical office based IT investments may prove practical, but they must first be developed, validated and provided.

*Develop outcomes-based simulation and decision models.* A strongly endorsed strategy was to develop one or more standard models to make preliminary outcomes and cost-effectiveness predictions. These may be artificial intelligence, expert systems or sophisticated data crunchers. Preferably, these would be modular, focused on medical practice, interactive and accessible to non-IT or outcomes experts and emphasize either societal or patient perspectives. Another alternative is to look to other fields for cost and benefit models for these preliminary predictions (e.g., environmental risk assessment).

*Increase investment in genomics.* Outcomes researchers are interested in the tremendous insight that genomics can provide and are eager to use this information to improve their studies. Most importantly, genomics can help refine the definition of appropriate study or target populations and end-points. Furthermore, if genetic information leads to tailoring and customizing of treatments, medicines, and devices, then outcomes research will have to be redefined to focus on the value of customization and tailoring, not on the specific chemical product involved.

*Leverage partnerships to expedite outcomes and clinical studies.* Establish partnerships between institutions that have steady funding and scientists who have a wealth of knowledge to create a balanced combination of resources. Furthermore, data sharing and exchange may speed-up research.

Outcomes studies are increasingly in demand, pivotal to clinical development and therefore more rigorous. In an accelerated learning system, they will play a significant role in reducing total health burdens on society and improving the productivity of health industries and organizations. In such a system, outcomes research will contribute to and benefit from a networked collaboration among all health stakeholders. The attending experts acknowledged the lagging shortcomings and encouraged the rapid adoption of the solution strategies.

The participants in the Outcomes Research small group were:

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## Section IV

### COMMUNITY-BASED STUDIES/BIOSTATISTICS

Clinical development in the future can better integrate research into ongoing medical practice to help providers and consumers learn more about both medicines and health. Community-based studies will gather information from the real world of medical practice, which unlike clinical trials cannot exclude people who introduce a multiplicity of variables. Population sub-groups that have historically been under-represented in clinical trials include the elderly, women, children and racial minorities. Community-based studies have the potential for developing information that is more specifically relevant for such sub-populations as well as other cohorts that may vary from the general population in other ways. Ultimately, these studies may create databases that provide more relevant information for any individual who wants to know what role a medicine may play in their overall health. A key need in realizing these potentials is to acquire appropriate cohort (comparison) - group information so that the effect of treatments, in either observational or experimental situations, can be validly assessed. Fully adequate methods for doing this do not yet exist, and need to be developed.

Statisticians understand that individual responses cannot be predicted based upon the mean response of a population. This “normalized data” based upon the average response of a population participating in clinical trials has provided the basis upon which society bets that a medicine will be safe and efficacious for any given individual. For those individuals who respond less than average, the information derived from the clinical trials may hold dubious value and the medicine may not be a good bet. The tradeoff for

society, however, has been that in order to learn about the product being tested, (and , in particular, to obtain the best chance of demonstrating statistically significant efficacy), clinical trials have leveled to minimize the variation from individual to individual. That tradeoff has been well justified historically, because the job of the physician is to observe the individual patient's response and tailor therapy accordingly. However, this alone may not be adequate in the future.

The intriguing question posed by the possibility of community-based studies is whether massive amounts of information about individuals can usefully, (economically and validly) be incorporated into the clinical development of products. Conceptually, as databases grow to include both more subjects and more variables, it becomes feasible to group sub-populations into multiple, "virtual" cohorts, defined by their shared relevant biological features.

For example, one biostatistical feature might be a genetic variation that results in "fast-metabolizers" and "slow-metabolizers" to a drug. Instead of using the general population as a single cohort, studies might incorporate phenotype information on an individual in order to determine whether the "slow metabolizers" or "fast metabolizers" have the best response (most effect, least toxicity). These studies would create a better basis for a patient to bet on whether the medicine would be safe and efficacious than a study that mixed the two cohorts together to determine the average response.

To this one example could be added a multiplicity of variables that might be relevant for an individual seeking to gain information from the experience of a larger group. Cohort analysis based upon sex, age, race, co-morbidities, and a host of other factors could be

performed if the databases for such analyses were large enough. The number of potentially important cohorts an individual might want to be able to draw upon to study their experience with a medicine could be very large, depending upon the kinds of questions that were important to ask. Questions that move beyond safety and efficacy, into side effects, economic tradeoffs and long-term vs. short-term benefits would call for data that, if it is collected at all today, is not yet integrated into clinical research.

To obtain useful information from all these situations, the problem of comparison groups must be solved; in particular -- where treatments are not assigned by some objective method such as randomization -- the confounding of treatment effects by disease effects. Unless reliable methods are developed, the voluminous results obtainable from large data bases may all be meaningless.

Improvements in community-based medical practice are building an information infrastructure that may support studies beyond today's clinical research. The same information infrastructure that provides electronic medical records, standardized protocols and provider report cards can also be used for clinical development, provided the methodology problems listed above can be solved.

Widespread use of the quality-of-life questionnaire, SF-36, for example, may link therapies to health gains that are invisible in current prospective studies. Beyond the physician's office, home-based monitoring and tracking of health status in fitness programs may offer potential sources for new biostatistics. Some health clubs, for example, are now monitoring the volume of oxygen in the blood as a measure of health and

fitness. Such data could provide new surrogate markers for health status, as well as a source for correlating exercise and different medical conditions. The current state of such community-based information sources is that they tend to be created in isolation, and for limited purposes—as are clinical trial databases. The future state could be very different.

Some visionaries now see how communities can integrate information coming from medical settings (inpatient and outpatient), homes and the other places where people work and play. Examples of such communities are only beginning to come on line. In Florida, Walt Disney's Celebration City has networked homes with fiber-optic links that reach out to hospitals and pharmacies. A number of companies working on this effort, including Anthem (which is tied to a number of Blue Cross Plans) and Health Magic, are in position to capitalize on advancing computers and communications technologies for health. Fiber optic cable now also links homes in New Brunswick, Canada, allowing immense volumes of data to be generated for each family member on a 24-hour basis. VAMP in the United Kingdom is also using linked computers to improve pharmaceutical utilization. These are only a few of the different companies and communities grasping the exciting possibilities that can improve clinical development - can we find other examples..

Biostatistics will deal with more descriptions of people and their illnesses in order to make “enhanced cohort data” available for community-based studies. More variables in the data can be used to form various pools for studies to dip into when specific cohorts are needed to answer a question. Standardized disease descriptions, for example, could be developed within different phenotypes. Randomization techniques can be used to create groups within the selected cohorts. These would be “natural” studies (also described more poetically as “clinical trials in the wild”) that could create a level of knowledge that

would translate into market intelligence. This intelligence should run far deeper than what is gained today from Phase IV clinical trials. Potentially this intelligence will reduce the need for Phase III clinical trials as well.

Adverse drug reactions constitute an area where large databases containing outcomes interpreted with the aid of new epidemiologic methods, could contribute greatly to the streamlining of new drug evaluation. It has long been recognized that the assurance with which new drugs can be approved for the market earlier in development is directly related to the thoroughness and speed with which our adverse reaction surveillance systems can detect and react to signs of trouble. (Alexander Schmidt, FDA Commissioner, 1974). As other roadblocks in the development and evaluation process are reviewed, our lack of a really good pharma vigilance system will become an increasingly important barrier to early approval. Solving this problem in the future, so that our large outcome databases can be intelligently used for post-marketing surveillance, could be one of the most important uses of these new data capabilities.

Consumers in smarter markets are expected to be far more powerful and active participants in the research endeavor to find new medicines and direct them appropriately into the marketplace. Working with health plans, consumers may be able to define the level of gain that makes it worth their risking participation in clinical research protocols that expose them to unknown problems. They should be able to enroll themselves directly into trials through the Internet, subject to the usual safeguards for validity of data integrity. Among the benefits anticipated from bringing research closer to consumers is the potential that treatment outcomes can more quickly be translated into new concepts for clinical development. Among the challenges is the question of whether consumers will

accept the responsibility of making decisions based upon information about risk. Fundamental regulatory change can only occur if consumers accept that certainty about safety and efficacy is an illusion and informed risk taking is an opportunity.

The group working on this topic identified the lagging and leading edges of community-based studies and biostatistics as well as strategies to advance progress.

### LAGGING EDGE

- The computers that doctors and consumers are using are often older machines that will not support the collection and exchange of large volumes of clinical data. Technology advances that make community information collection and dissemination possible are slow to move into the medical system, making access to information a serious issue.
- Revolt over sharing medical data is already underway. The fear that privacy will be disregarded and medical information misused creates a significant lag when it fosters regulation that blocks progress. Mistakes that are made by those who collect and use medical data are going to increase the fear factor.
- Confusion over the scientific basis of regulatory inferences creates a lag in public understanding of safety and efficacy evidence coming from specialized population data. Such data does not provide knowledge about individual patients, and its predictive value is often misunderstood.

### LEADING EDGE

- We have models from which we will learn such as Celebration Health (Disney), the ethernet created in New Brunswick, Canada, and a variety of pilot projects in community and managed-care settings.
- Advanced biomonitoring devices are being created by government agencies, such as the Advanced Research Projects Agency (ARPA), the Department of Defense and by companies.
- Fitness center monitoring is creating databases built around markers for health. These databases are often maintained by individuals over a period of years, and they incorporate physical measures (weight, resting pulse, etc.) that in some cases now includes blood tests for oxygen levels.
- Patient-centric care models have developed in nurse and nurse-practitioner education and care delivery, as well as in the Indian Public Health System. These models use a paradigm that makes the care of each individual paramount, rather than focusing on average population characteristics.

### STRATEGIES FOR PROGRESS

*Engage and incorporate patients more fully into clinical development.* Each patient can and should contribute more to the knowledge base that will serve other patients who have similar symptoms and decisions over therapy. The differences that belong to each individual creates a potential source of learning about genetics and phenotype, as well as specific behavioral and value factors that relate to health. As patients engage in overcoming disease in the pursuit of health, they have an opportunity to join in the quest for knowledge that helps both them and



others. By engaging more of the public in this pursuit of new knowledge, the medical research community will have a greater capacity to overcome many of the existing barriers to improved clinical development.

*Elucidate and standardize disease descriptions and diagnosis within genotypes and phenotypes.* A far better understanding of genetics will provide us with additional knowledge about diseases that can move us toward customized medicine. To refine the standard disease descriptions, an effort should be made to develop specific descriptions that include information on genotypes and phenotypes. ICD-9 codes describe more than a thousand human ills that represent a huge diversity. The compendium of drugs includes 40 major categories. Yet cutting across these standard descriptions is a huge variance of disease susceptibility and treatment response. More specific standards can foster better care and better research. Customization of care can now be characterized as the “art of medicine.” Clinical development can systematically improve this art with knowledge about population cohorts that supports better targeting of medicines to account for individual differences within the general population.

*Interface the new “relaxed” approach with the “gold standard”.* The knowledge that we have gained from years of clinical development using the “gold standard” of double-blind, placebo-controlled studies needs to be integrated with community-based studies, using methods/improvements yet to be developed, as described above.. The tremendous confidence gained from the most objective studies should be a foundation for future learning that incorporates new methods

and increases the range of applied biostatistical techniques. The foundation can be further strengthened by improving efficiencies within the framework of current clinical trials, even as new methods with comparatively “relaxed” standards of evidence are used to extend today’s knowledge.

*Develop feedback in order to create a learning system.* Clinical development, community-based medical practice and patterns of everyday life can be tied together in a learning system by information feedback loops. Current feedback loops exist (e.g., medical journals, adverse drug reports, epidemiology and others) but are inadequate. Larger volumes of information can move at faster speed to make possible the new discussions of integrated health systems that are emerging in this country and elsewhere. Efforts to consciously design feedback systems that tie medical research, practitioners, patients and consumers in a continuous learning process can accelerate the transition to 21<sup>st</sup> century clinical development.

There are many questions that will have to be addressed to design a more powerful learning system. Will this be one unified system of information or various systems without congruence? How will we manage the data and what type of quality control will be in place? How can we assure that everyone who relies on this system understands the information that is being provided? Technical, scientific data will have to be translated into consumer terms that allow patients to understand the information. Undoubtedly, patients will need clarification of information in real time. How much can be done electronically? Designs for patient information systems should provide service that answers questions for patients anytime, anywhere.

The group working on the Community-Based Clinical Trials/Biostatistics included:

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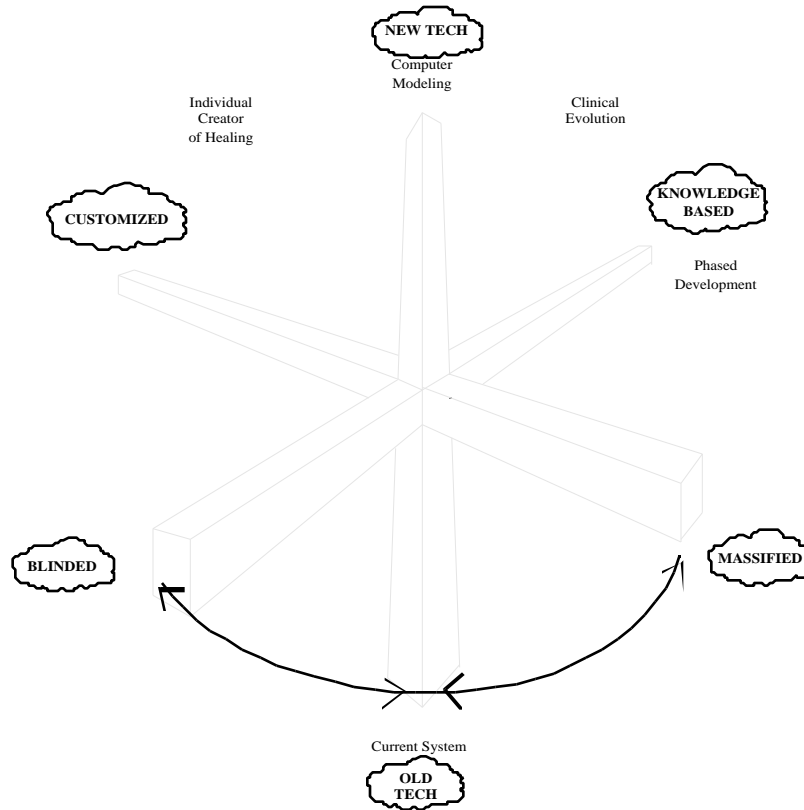
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## Section V

### THE EMERGING PARADIGM



Having begun with the proposal to take “a systems view from the future” for planning progress in clinical development, we were almost forced to step back from the work presented by the four small groups. Each began with the desire to have clinical development embody “combined principles and processes of ‘healing’, ‘learning’ and ‘creating’.” Each showed paths of progress. But where had we arrived? We had to step back from the particulars to find an emergent pattern—a new paradigm, or mental model for the path of future development.

The graphic on page 42 provides a picture of the paradigm we saw emerging from the different discussions of change in clinical development. Change is working along different dimensions. Movement along each dimension is uneven, coming at different rates and often in fits and starts. Some of the change is far more subtle and conceptual, while other forms—technology, for example—leap out and are impossible to ignore.

Even though the technology dimension is obvious when we look at computers, the variable speed of adoption can be overlooked. At the leading edge, supercomputers work on complex models of molecules, weather systems and battlefields. However, in the current clinical development system, desktop and mainframe computers have yet to take full advantage of the computer's ability to speed and improve processes. Even the leading edge of clinical development has yet to take advantage of the fastest computers and the best minds in software. The lagging edge is working with outmoded, unconnected computers, or worse yet, with massive volumes of paper rather than computers. Both edges will move forward between now and 2005, and both need attention. Resources should go to the computer simulations that can provide new ways to validate and extend our knowledge. Dollars should also be spent to increase the efficiency of tried and true methods in clinical research.

Along with computers, molecular genetics will move clinical development into the future. The most exciting path takes us from “massified” to “customized” knowledge. The massified view sees each person as the same, while customized knowledge strives to recognize any individual difference that can make an improvement. Computers allow us to recognize more variables, and molecular genetics can help us identify the variables that

are most important for human health. In recent years, for example, it has become clear that different genetic groups metabolize medicines at different rates. In future years there will be many more discoveries about what makes one group of people different from another. This knowledge is filled with promise for shifting our focus from products to people and the outcomes they seek. Moving farther on this “customized” dimension may someday take us to medicines tailored for each person. This kind of movement can only occur if both science and regulation recognize the individual as the center of the system.

The final dimension of moving from a “blinded” to a “knowledge-based” system is probably the most subtle and difficult to recognize. The current system is built around objective confirmation of information with the most concrete forms of data possible, and is highly suspicious of endpoints based upon subjective factors. The real world that this system is designed to serve is filled with subjective responses, and people who look for outcomes that they evaluate subjectively. In physicians’ offices, nursing conferences and homes the objective forms of information and subjective knowledge come together and decisions are made. The knowledge that comes from a combination of objectivity, data, subjective involvement and intuition works, but in a piecemeal fashion. Parts of the system hold data paramount, while other parts celebrate the caring word or the healing touch. In the fragmented world of today, that is how the system works. Now people look forward to integrated health systems, which may use biotechnology, genetic surgery, prayer and alternative therapies in various combinations. If this is the future, today’s fragmented world will need feedback for all the pieces to come together around learning healing and creating.

## Section VI

### NEXT STEPS

#### GATHER SUPPORT

Identify leaders whose interest in accelerating progress would lend support to a concerted effort, whether approached as a series of small steps or a large, “Manhattan Project” that gathers resources and talent. The potential leaders should come from various business sectors that can profit from improvements in clinical development, as well as from the FDA and other government agencies. The pharmaceutical industry is an obvious stakeholder, but so too are clinical research organizations, although either would have to dare to break the mold that is formed by current practices.

Computer consortiums are a less obvious, but clearly interested group that should be drawn into a leadership role in the collaboration to advance clinical development. Computer and communication pioneers can make one of their greatest contributions to life in the 21<sup>st</sup> century through this effort. Many people in this field also have successful experience in partnering between companies and governments to develop advanced software and hardware standards. These partnering skills will be essential to success in moving the current system forward.

Turning to the public sector capacity to lead a change effort, the FDA represents a key part of the larger public health sector that must play a key role. Other leaders in public health at the state and local level will also be needed. The role public health officers play in surveillance, epidemiology and medical records makes them key players, particularly as

managed care and integrated delivery systems grow. The partnership with consumers and patient groups in the service of advancing knowledge and innovation is best formed through the offices of public health agencies. FDA can be encouraged to lead other public health agencies into the effort to integrate clinical development at the community, state, national and international levels. As an acknowledged lead agency in the international arena, it would be particularly valuable to have the FDA engage other national regulatory bodies in the discussion of a future evolution for clinical development.

The FDA will need Congress to support a leadership role for the agency, and to participate in a change process. Authorization, legislative language and wise oversight will be key ingredients for any successful change in clinical development. Therefore, congressional leaders—both Members and professional staff—must be enlisted in efforts to improve the system.

## SET GOALS

In order to coordinate the efforts of both public and private organizations, a key step can be to create audacious goals for improving clinical development. Two goals appear ambitious, but plausible, given the developments discussed in this meeting: to cut costs in half by 2005 and to reduce the time between discovery and entry into the market by half. Many pharmaceutical executives today estimate that the development of a new medicine can cost \$500 million, and in private conversations knowledgeable people have said the cost can approach \$1 billion.

The goal of reducing the time from discovery to market may actually be more important economically, however, than the goal of reducing the costs of research. While fast-track projects have moved products from lab to pharmacy in 6 years or less, 10-to-14 years are probably average development times. Patents are applied for early in the development process, so reducing the time of development for a new medicine by 50 percent can mean additional profits for products that may be substantially larger than research costs. Extending the patent protected life of a blockbuster medicine that has \$1 billion sales per year will provide even greater returns to research-based companies than the substantial savings possible from the reduction of clinical studies.

Equally audacious goals can be set for progress in science and technology that is integral to clinical development. The goal to have all mapped human genes used to customize medicines and to have pharmaceutical developers and regulators given primary access to high-speed (5 teraflop?) computers by 2005 signifies serious intent. Society's commitment to the human genome project was signaled by large-scale public funds committed over a long period of time to meet the goal of a complete map by 2005. The likely accomplishment of that goal is feasible in large part because of the powerful computers that are harnessed to the tasks of identifying and sequencing genes. The fruits of the public investment in this research effort can best be harvested by the development of new medicines, diagnostics, preventives and enhancement products. The goals to keep the pharmaceutical sciences at the leading edge of genetic and computer advances may provide the best possible basis for the public and private partnership that will advance science in the public interest.

Another goal can be to create a “big-picture roadmap” that places clinical development into relationship with other systems of “healing, learning and creating” so that feedback can optimize evolution. This end-to-end model should show how healing promotes new learning that helps others. The learning then leads to creating new innovations that fosters healing in new areas of need. This model might first be used to show how treatments can develop faster and better, and then be used to show how any healing behavior can be promoted throughout the population. This model can be widely distributed to all actors throughout the system in order to develop shared understanding that accelerates progress.

A related goal will be to reduce costly litigation and unnecessary regulation that results from the lack of trust. Shared understanding can form public and private partnerships in the endeavor to improve healing, learning and creating of new therapies. The stronger the partnerships, the less likely it will be that people will resort to legal mechanisms that run up the costs in the system. To some this goal appears tangential to clinical development. Yet others see the level of change reaching deep into our culture, and the current culture of litigation appears inhospitable to the future innovations we are seeking. Culture has always defined the bounds and thrust of research on humans. The level of learning, healing and creating that is needed reaches deep into our culture, making the goal to reduce legal battles an important aspect of this work.

## DEVELOP A FORUM

The next step we are taking is to develop a forum through which to identify specific examples of progress in clinical development and encourage further collaboration. There

are significant examples of progress already, including the International Conference on Harmonization (ICH), the Collaboration on Drug Development Improvement (CDDI) and the work between industry associations and the FDA on user fees and computer-assisted new drug applications (CANDAs). The proposed forum will be dedicated to learn the lessons of success and apply them in areas most likely to advance clinical development.

This draft report on those areas will be circulated to gather comments from interested parties. Participants in the meeting will be invited to distribute copies of a revised draft of the report. IAF will seek further funding for a second meeting to further the discussion with those who participated and others. Suggestions for improvement and new ideas are welcome. We look forward to new participants, and invite all who are interested to join and help move clinical development into the 21<sup>st</sup> century.

## APPENDIX

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