# RETHINKING THE APPROACH TO EXPANDED ACCESS PROGRAMS

REPORT OF A FORUM FOR COLLABORATIVE HIV RESEARCH ROUNDTABLE DISCUSSION

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## EXECUTIVE SUMMARY

Expanded access programs (EAPs) are a critical component of antiretroviral drug development. They provide patients who have few or no therapeutic options with early access to new therapies and extend the reach of standard clinical trials to those patients who may not be able to enroll in clinical trials because of exclusion criteria or geographic access. There is little question that EAPs have contributed to the survival of many patients since the first antiretroviral agents approached marketing approval in the late 1980s. EAPs have continued to play an important role in the HIV treatment arena as the HIV epidemic and antiretroviral treatment landscape have evolved, with substantially more treatment choices and dramatically improved effectiveness.

The Forum for Collaborative HIV Research convened a roundtable meeting on February 16, 2007, that brought together clinical researchers, community advocates, and both industry and regulatory representatives to review the current role of EAPs in HIV drug development and treatment. The primary goal of the meeting was to discuss how current and future EAPs might be improved so that they best meet the needs of patients, clinicians, industry sponsors, and regulatory agencies.

While the roundtable was primarily focused on the workings of EAPs in the United States, several representatives from Europe participated in the meeting and added their perspectives to the discussion. Like earlier phases in drug development, providing early access to investigational drugs is a global issue. Given the variety of regulatory structures in different countries across Europe, the system of EAPs there is considerably more varied and complex than that in the US. While this presents a challenge to companies who are developing EAPs on a global scale, it also provides opportunities to look at alternative systems that may help to improve the existing EAP structure in the US.

### Meeting Format

The meeting began with brief presentations that outlined the advantages and disadvantages of EAPs from various perspectives. These presentations identified many of the key issues and provided a baseline framework for the day's discussion, including issues common to all

stakeholders, and issues with differing perspectives among the various constituencies represented by the Forum. These discussions set the stage for the development of basic recommendations regarding future directions. In general, they reflected the overall consensus among the meeting's attendees that EAPs continue to provide benefit to patients by providing early access to investigational therapies for the segment of patients who are without treatment options.

The discussion was framed by a series of questions that looked at EAPs in terms of need and access; Internal Review Board (IRB) issues and risk:benefit; and site-related issues.

Need & Access

- Are EAPs still necessary in the current antiretroviral treatment landscape?
- What patient population has access to drugs through EAPs?
- What are the barriers for patients to access an EAP?
- What sites participate in an EAP?
- How valuable is the information gathered in EAPs?

IRBs and Risk:Benefit

- What are the IRB issues?
- What are the risks?
- What are the benefits?
- What are the contract and liability issues?

Site Issues

- Should there be reimbursement for sites participating in EAPs?
- Do EAPs slow enrollment into other clinical trials?

**Identifying the Issues**

From the morning's presentations and the ensuing discussions, the participants identified a number of key issues.

- The size of the patient population that currently needs access to investigational antiretroviral drugs is difficult to estimate. Such patients do still exist and the size of the population is probably decreasing, but convincing data to indicate the number of patients in need of early access is lacking. In addition to the criteria of failing a third regimen, a key factor in the equation is the urgency of the patient's need for new therapy.
- Tension exists between the clinical and research aspects of EAPs. While the primary rationale for EAPs is to provide early access to investigational drugs for patients in need, secondary competing interests are in play. These include the collection of useful safety data that might identify unknown safety issues and ultimately help guide treatment strategies. However, current data collection practices rarely yield useful information.
- EAPs are associated with a heavy administrative burden that limits the ability of some sites to participate; in addition, these programs are unfunded or underfunded. The burden appears to be particularly acute in the academic research setting, where intensive IRB approval and oversight combined with the data collection requirements of the protocols has forced some centers to forego participation in EAPs until they can find a mechanism to compensate for the burden. As sites refuse to participate, this limits patient access to the EAP.
- EAPs need to be conceived of within the context of clinical strategies overall. As the HIV epidemic and antiretroviral treatment strategies have evolved, it is no longer advisable to give patients new drugs without ensuring other active agents in the regimen. Otherwise patients would effectively be receiving virtual monotherapy and risk the development of drug resistance and subsequent regimen failure.
- Geographic limitations continue to impede access for patients in small cities and rural areas. Ideally, the system should be able to provide access to experimental drugs for all patients who need them and qualify for EAPs regardless of where they live.
- Information about the EAPs can be quite difficult to find. Some companies do not list sites participating in their EAP on their own websites or on database websites like clinicaltrials.gov, making it very difficult for patients and their physicians to know where they might access experimental agents outside of clinical trials. Similarly, companies may not adequately advertise the existence of their EAPs. Industry is particularly concerned about the perceived appearance of pre-approval marketing.

There was general agreement among all of the participants with regard to the issues that are most relevant to any rethinking of the current EAP structure. If any tensions exist in the current EAP framework, they appear to emerge out of the operationalization of the EAP protocols, rather than from differences in the priorities and principles of the stakeholders. While the roundtable was not intended to design new rules for the administration of EAPs, the participants were able to identify a few key directions for potential improvement.

- Explore the potential for standardization of EAP data collection requirements and safety reporting. This could reduce the redundancy in the current system and simplify participation in multiple simultaneous EAPs. This would particularly apply to the reporting of events to IRBs.
- Explore the potential collaboration between the FDA and other regulatory bodies to standardize and minimize the burden, as much as possible, for the very complex and variable regulatory requirements for EAPs.
- Explore how the pharmaceutical companies can standardize their EAPs in terms of development of case report forms and adverse event reporting.
- Provide guidance to contract research organizations (CROs) on data collection requirements such that the administrative burden for an EAP is reduced compared to a standard clinical trial.
- Apply and take advantage of technological modernization in adverse event reporting. For example, a centralized electronic database could provide access to basic tabulation and analysis of the voluminous serious adverse event reports that in their present form are virtually useless to the individual site investigators and site IRBs.
- Consider further collaboration between regulatory agencies and the pharmaceutical companies in the design of EAPs to include the simultaneous use of multiple investigational agents and to identify creative study designs that will limit the use of virtual monotherapy and address the evolving therapeutic needs of patients.
- Consider a two tiered expanded access approach: one would be an actual research protocol designed to address specific questions leading to approval, and which would be appropriately reimbursed like any other clinical trial. Such a protocol could address the types of issues normally studied in Phase 4 studies. These could be designed to target underrepresented patient populations. The second parallel approach could be a simplified protocol, similar to the

current EAP protocols. However, both tiers likely would need reimbursement to participating institutions due to non-recovered costs of participation in the EAP.

The participants observed that this roundtable meeting represented the first opportunity to engage in open dialogue with all of the relevant parties to talk about improving expanded access programs for antiretroviral agents. As such, it was a valuable opportunity not only to listen to the concerns of their colleagues but also to realize how much their interests align in support of providing access to therapies for patients with few treatment options. In addition, the meeting was particularly timely given that the FDA recently (on December 16, 2006) proposed new rules for the regulation of EAPs and is currently seeking comment on the propose rule changes.

The following report summarizes the proceedings of the roundtable, with a particular emphasis on identifying the issues and challenges around the operation of EAPs in their current form. It is not meant to be a complete, thorough review of the development and implementation of expanded access programs, but by identifying key issues, it represents a starting point for future discussion of the topic.

## BACKGROUND

### BRIEF HISTORY OF EXPANDED ACCESS PROGRAMS

Expanded access programs were developed in order to make promising investigational treatments available to patients who need them as early in the drug evaluation process as possible. In particular, the goal is to make such drugs available to patients who have exhausted all currently approved therapies. Early in the HIV epidemic, HIV activist organizations challenged the existing drug approval system as too cautious, particularly in the face of a deadly epidemic that was claiming thousands of lives for lack of effective therapies. Their efforts shifted the balance from the strictly protective model with an emphasis on preventing harm to patients toward increasing access to potentially effective therapies for patients who are in need.

There are a number of mechanisms through which patients may obtain access to unapproved therapies. Clinical trials make up the most common way that patients receive drugs before they are approved. Given the controlled nature of clinical trials, which are designed to look at very specific efficacy and safety outcomes, enrollment qualifications are generally highly selective, limiting enrollment only to those patients who meet strict entry criteria. In addition to clinical trials, there are a number of expanded access mechanisms by which drug companies can make unapproved drugs available to patients in need. These include

- Open-label studies
- Treatment IND protocols
- Parallel track protocols
- Single patient IND or emergency IND

Historically, it has been the mission of the FDA to protect consumers (and the public health) from harm by ensuring the safety, efficacy, and security of drug therapies. The 1962 Kefauver-Harris Amendment to the Food, Drug, and Cosmetic Act, which was enacted in response to the near-approval of thalidomide in the US, defined the role of the FDA in protecting public safety by strictly controlling the approval and marketing of drugs for humans. In that case, the US

approval of thalidomide was averted as a result of the emergence of data indicating a risk of birth defects attributable to thalidomide in European studies. This episode strengthened the protective role of the FDA in the drug approval process, but the increased scrutiny of the approval process eventually led to a delay in drug approvals in the US compared with other countries.

The emergence of the HIV epidemic, and the subsequent organization of HIV activists, increased public awareness of the consequences of delaying drug approval. HIV activists argued that they were willing to accept the risks associated with early access in exchange for the potential life-saving benefits the drugs could provide. The FDA responded to the demands of HIV patients and clinicians by streamlining the approval process for drugs for serious and life-threatening conditions and by codifying mechanisms for providing access to drug therapies prior to their FDA approval. As a result, in the late 1980s and early 1990s, thousands of patients accessed the nucleoside agents that were progressing through clinical development. The expanded access programs (EAPs) for zidovudine and didanosine occurred via the treatment IND pathway, which allows access to drugs that have demonstrated some level of efficacy and safety [1] The clinical experience in these large trials provided useful clinical information that was subsequently published in the literature [2] [3].

The FDA also responded to the demand for antiretrovirals by revising and updating the approval process. Beginning in 1987, the review of HIV medications received the highest priority at all stages of the approval process. The agency also developed an expedited review process for HIV medications, which has improved to the point that the FDA now frequently approves HIV medications for use in the US before virtually any other country.

***Case Study: The Zidovudine Experience***

After the initial phase 2 study of zidovudine was terminated in September 1986 (due to a demonstrated short-term mortality benefit across all strata receiving zidovudine), it was recognized that a mechanism was needed to make the drug available to critically ill AIDS patients while the study data were analyzed and the FDA completed its review (which was expected to take another 6 months). The FDA established criteria for a Treatment Investigational New Drug (IND) for zidovudine, permitting access to the drug within a week of the trial's

termination [2]. Between October 1986 and March 1987, more than 4,000 patients were treated with zidovudine through the treatment IND program. The zidovudine treatment IND included patients with prior PCP (Pneumocystis Carinii Pneumonia) who were considered to be at increased risk of death before drug approval. The investigators made an effort to collect high-quality data, and although data collection was imperfect, it was eventually published, showing a mortality benefit in this highly advanced patient population [2].

The zidovudine treatment IND protocol resulted in the codification of the criteria for treatment INDs. Treatment IND was established for drugs that treat serious life-threatening diseases with no comparable alternative drug available. In addition, a drug must have demonstrated positive results in clinical trials (phase 2 completed and phase 3 ongoing) and have accumulated adequate safety data. Patients may be eligible for a treatment IND if they are not eligible for the definitive clinical trials. The pharmaceutical company must apply for treatment IND status as a bridge between trials and approval [1] [4]. This is the same mechanism used for the larger expanded access launches used with HIV drugs today.

In 1991 the Institute of Medicine published a report based on a roundtable that identified some early concerns about the use of expanded access programs in HIV. They suggested that EAPs might potentially be a burden on companies' future profits by raising safety concerns, increasing the cost of drug development, and increasing the risk of product liability. An additional concern was that the access to treatments via EAPs could lead to a disincentive for patients to enroll in clinical trials [5].

The early antiretroviral EAPs were large, reflecting the significant need among patients in the late 1980s and early 1990s (Table 1—Antiretroviral Expanded Access Programs). Due to difficulties with drug production, the EAPs for the early protease inhibitors were substantially smaller. By the time efavirenz was available through an EAP, clinicians had recognized the risks of adding an NNRTI (non-nucleoside reverse transcriptase inhibitor) alone to a failing regimen and the EAP required the use of at least one other active agent in addition to efavirenz [6]. Three concurrent expanded access programs allowed coenrollment with the investigational drugs: abacavir, adefovir and efavirenz.

According to research by the Forum for Collaborative HIV Research, the numbers of patients participating in expanded access programs is decreasing since 1998. In addition, there are disproportionately few women and persons of color participating in EAPs (Figures 1 and 2). The information about EAPs is not easy to gather, as there is no central repository. The information is spread among many sources, and for past EAPs there may or may not be information publicly available.

While the ultimate goal of an EAP is to make a drug accessible to patients in need, the data collected during some past programs have been published in journals and presented as abstracts at major scientific meetings. However, data collection has been inconsistent (e.g., in the tenofovir EAP, 70% of the patients for whom data were presented at the 13th Conference on Retroviruses and Opportunistic Infections had no CD4 count noted), making it difficult to draw many meaningful conclusions [7].

***A Potential New Model for Expanded Access Programs***

One potential new model for EAPs is to institute a more systematic approach wherein treatment INDs are not the norm. While EAPs could be allowed in specific circumstances (e.g., for patients with advanced disease that is seriously life-threatening or for individuals who do not meet eligibility requirements of clinical trials), it may be preferable to replace EAPs with expanded clinical trials (Figure 3—Potential New Model for Expanded Access Programs). This way, patients could be provided early access to drugs while providing solid clinical data that would contribute to the scientific database about drug safety, efficacy and drug interactions.

Ideally, such a system would provide access to more than one experimental drug at a time, providing patients with the opportunity to receive combination therapy with several potentially active drugs (e.g., the DUET study from Tibotec, combining etravirine and darunavir). This will require promoting collaboration between pharmaceutical companies and finding a way to link the EAPs of multiple drugs. Such studies could provide important data with regard to efficacy, pharmacokinetics, drug interactions, and overlapping toxicity data. Further, the data from these trials could be disseminated via web-based networks.

## CURRENT APPROACHES TO EXPANDED ACCESS PROGRAMS

One of the primary stated goals of the EAPs has been to provide earlier access to drugs for patients who need them. There is little question that earlier access to a drug can benefit those advanced patients who are in desperate need of effective therapies.

At present, the approach to EAPs is to have each company's program (independent of other companies) precede the staggered release of new antiretrovirals prior to FDA approval. Given what is known about the development of drug resistance, it can be argued that using EAPs to add a single new agent to failing regimens results in "virtual monotherapy," increasing the risk of resistance and potentially leading to transient response and reduced long-term durability. In addition, there are risks associated with using untested combinations of drugs before the potential for drug interactions has been systematically studied.

While the early expanded access programs were instituted to get drugs to patients who needed them as early as possible, more recent EAPs are open for shorter periods of time in part because the approval process has been expedited and drugs enter the market more quickly. At present, most EAP programs are lasting less than 1 year (e.g., the darunavir EAP lasted from October 2005 to June 2006).

In addition to earlier access, the EAPs have the potential to provide access to drugs for patients in need who are not able to enroll in clinical trials due to geographic limitations (i.e., not being near enough to a study site). However, a similar problem arises with EAPs themselves, in that a patient needs to be within range of an approved EAP site to participate. This has led some advocates to ask whether there may be a more effective and equitable mechanism for providing early access that may benefit patients more broadly.

The following section of the report presents highlights of the brief presentations from each of these points of view that provided a foundation for the day's discussion. In most cases, the presenters summarized both the benefits and limitations of the current EAP structure.

## PATIENT/COMMUNITY PERSPECTIVE

From the perspective of the patient community, substantial improvements have been made in the design and coordination of EAPs in recent years. For example, increasing collaboration between pharmaceutical companies has allowed the simultaneous use of multiple investigational agents in phase 3 studies and EAPs. Some examples of collaborative trials include:

- Darunavir + TMC125 (etravirine) phase III (DUET study)
- Darunavir EAP + MK 518 (raltegravir) phase III (Benchmark study)
- Raltegravir EAP + etravirine EAP (present)
- In the near future: maraviroc EAP + raltegravir EAP + etravirine EAP
- ACTG 5241 (in development): a regimen composed from a menu of recently approved drugs (darunavir, enfuvirtide, tipranavir) and investigational drugs (etravirine, maraviroc, raltegravir). Study participants will be randomized to one of these multi-drug regimens with or without nucleoside reverse transcriptase inhibitors.

Patients are particularly enthusiastic about the fact that, with three new agents coming to market in the same time period, it will be possible for highly treatment-experienced patients to enroll in up to three concurrent EAPs. Along with the two recent additions to the armamentarium from existing drug classes (the PIs (protease inhibitors) tipranavir and darunavir), as well as the fusion inhibitor enfuvirtide (T-20), the newest investigational drugs from two new classes make up a second wave of ART, with which more patients potentially will be able to construct viable regimens for the first time in several years.

Community advocates are encouraged by the emergence of more user-friendly EAP websites that allow for improved access to information about EAP sites and inclusion/exclusion criteria for both patients and clinicians. Similarly, one company is reaching out to non-traditional sites, including those that may not have prior EAP experience. It is hoped that this will improve access to experimental therapies for uninsured patients and traditionally underserved populations. In addition, drug companies are beginning to invite contract research organizations (CROs) to community review meetings, providing an opportunity for community advocates to ask questions

about aspects of EAP protocols that impact patients and are not necessarily reviewed by the sponsoring drug company.

**Challenges**

Geographic limitations continue to impede access for patients in small cities and in rural areas. Ideally, the system should be able to provide access to experimental drugs for all patients who need them and qualify for EAPs regardless of where they live.

An ongoing issue is the difficulty of accessing information about EAPs. For example, some companies do not list their EAP sites on their own websites or on database websites like clinicaltrials.gov, making it very difficult for patients and their physicians to know where they might access experimental agents outside of clinical trials. Similarly, companies may not adequately advertise the existence of their EAPs. Industry is particularly concerned about the perceived appearance of pre-approval marketing, but it is critical that patients and physicians be informed about the availability of experimental agents outside of the clinical trial arena.

On the clinical side, community advocates express concern that not all EAPs require drug resistance testing at entry, which can increase the risk of virtual monotherapy for patients starting an investigational drug in existing drug classes. Another concern is the lag time that occurs between the initiation of EAPs and relevant pharmacokinetic and drug interaction studies. This can result in patients being exposed to unknown safety risks and the potential for impaired efficacy or increased toxicity resulting from the combination of one or more experimental agents with background therapies.

Another concern for all is that as a result of the costs and manpower requirements associated with EAPs, many physicians and clinics decline to participate. In particular, the existence of multiple concurrent EAPs may result in too great a burden on staff time with little or no reimbursement for that time. If local sites decline to participate in the programs, access for patients could be severely limited.

**European Experience**

In addition to examining the working of the EAPs in the US, it is valuable to consider the way expanded access programs are handled in Europe and other parts of the world. For the purposes of the discussion, a brief presentation outlined some of the concerns among patients in need of investigational therapies in Europe. One of the key points of the discussion is that the experience in Europe varies widely among the different countries. While there are many patients who are failing their current regimens and who do not have access to new drugs, they are often much less visible that they used to be. This is attributed to the fact that they frequently come from underserved communities including ethnic minorities, undocumented migrants, and sex workers.

Many groups have suggested that there needs to be a standardization of guidelines for access to investigational drugs. For example, after drug applications are submitted to the FDA and to the European Medicines Evaluation Agency (EMEA), perhaps the FDA and EMEA should be responsible for setting up guidelines for who should have access to these drugs. In this way access might be less dependent on individual situations and clinicians. Expanded access programs continue to be an important instrument for patients who do not meet criteria for clinical trials and who have no other options to gain access to life-saving drugs.

The problem of virtual monotherapy has also been reported in Europe. An ongoing issue is the need for better training for physicians on how to prescribe antiretroviral drugs. This is particularly a concern in poorer countries.

Ultimately, the biggest problem from the community perspective in Europe is the lack of access to treatment for many HIV infected people. A result of this is that many patients enter treatment very late in the disease, with the result that they are more sick and in need of more substantial treatment.

## PHYSICIAN/PROVIDER PERSPECTIVES

### ***The Academic Center***

For one example of the physician/provider perspective, we looked at how EAPs have developed at Johns Hopkins University (JHU) in Baltimore. At JHU, the administration of EAPs originally fell on the shoulders of the JHU research unit, because it was recognized that the research unit

had both the administrative and clinical skills necessary to manage the EAP protocols. However, it quickly became apparent that the research unit was being overwhelmed by the substantial enrollment of patients in the EAPs and the significant administrative requirements of the EAP protocols. For example, at the time of the simultaneous abacavir, adefovir, and efavirenz EAPs, the research unit limited their engagement in normal clinical trials in order to manage the EAP burden. While it initially made some sense for the research department to manage the EAPs, given their clinical trial experience, it rapidly became clear that, since EAPs are primarily a clinical (rather than research) undertaking, the cost of running the EAPs should not be borne by the research department. Furthermore, the fact that EAPs used a substantial amount of department resources and provided no reimbursement was a financial disincentive.

As a result, although JHU has a major HIV center and pressure to offer access to investigational agents to patients is strong, JHU, like many other academic centers, has opted out of participating in EAPs in recent years because the issue of how to pay for the staff and administrative expenses has not been satisfactorily resolved. The JHU involvement in earlier EAPs came close to bankrupting its clinical research operations.

However, the simultaneous emergence of three EAPs for raltegravir, etravirine, and maraviroc, has forced JHU to reconsider its position on participating in EAPs, particularly when they involve important new drugs. JHU is now participating in the ongoing raltegravir and etravirine EAPs because of the importance of these drugs for treatment-experienced patients. However, mechanisms for funding these programs remain in question.

Some of the current EAPs do offer minimal financial compensation. However, academic centers incur substantial administrative overhead costs and the reimbursement does not come close to covering the costs of managing the EAP.

Another issue that is of concern is that the availability of multiple EAPs may impact on the ability to carry out research, in part because providers may be hesitant to submit their patients to randomization required by clinical trials when they know that they can get the drugs through an EAP. This means that researchers are less able to recruit patients into the clinical studies.

In summary, although there is no question that EAPs benefit patients who need access to new therapies, academic centers are concerned about the strain that they put on research departments. Acknowledging that EAPs are not research in the traditional sense, there needs to be a revenue stream to cover the costs of operating these programs.

***Private Practice***

Another perspective on EAPs can be found among the clinicians who participate from within private medical practices. Private practices may not have the same level of administrative overhead as an academic center (in terms of IRBs and approvals), but participation in EAPs requires substantial administrative and record keeping capabilities regardless of the clinical setting.

Nevertheless, many private practices participate in EAPs because they are dedicated to providing the best care available to their patients. EAPs provide a way to offer promising new drugs to patients who are without other therapeutic options. In fact, although this is becoming less common today, many physicians have patients who have survived because of the access to treatments obtained through EAPs.

It is important to keep in mind that beyond those patients whose virus population is resistant to all available antiviral drugs, access to investigational drugs may be necessary as a result of toxicities associated with current therapies. This, too, is a legitimate reason for providing access to experimental agents.

**Challenges**

From the private practitioner's perspective, the complexity of EAPs can be daunting. In particular, the data collection requirements can be overwhelming, requiring trained research staff to administer the protocol in much the same way as with a standard clinical trial. This is an argument for treating EAPs that have substantial safety data collection requirements as standard clinical trials, with reimbursement to sites for the administrative work that is involved. As noted above, the presence of concurrent EAPs can be a significant drain on resources. This has to be

balanced against the benefits of having multiple new agents available for patients who need them.

An additional concern with those EAPs that have limited sites is the need to accept patients from outside an individual practice. This can present difficulties related to trying to manage patients with unknown treatment histories.

## THE PAYOR PERSPECTIVE

The large payor environment includes many treatment-experienced patients who are in need of early access to new agents. Given that not all patients will qualify for clinical trials, EAPs provide a mechanism for making these drugs available to patients in need. Without the early access to new drugs, prior to approval for marketing, a segment of patients would likely end up on inferior regimens. Network physicians appreciate the potential to gain early experience with new drugs, and also like the opportunity to participate in programs that while perhaps not as rigorous as a standard clinical trial, satisfy clinicians' desire to stay involved at some level with clinical research. With this involvement may also come better relationships with pharmaceutical companies and the possibility to develop an organization's credentials as potential sites for phase 3 and 4 clinical trials.

Recognizing that healthcare insurance is also a customer-driven business, another advantage from the payors' perspective is that early access to drugs improves the satisfaction of their patient-customers. Patients appreciate knowing that their clinicians are offering the most up-to-date treatment options.

Looked at from the financial perspective, participation in EAPs can save payors money. Data from Kaiser Permanente indicate that individual regions estimate their cost savings to be at least $100,000 per year from participation in EAPs. These savings are based on estimates of the costs of drugs accessed over time according to the post-approval purchase price. Participation in EAPs may also contribute to better overall care for patients with more advanced disease, resulting in fewer costs associated with that care in terms of reduced opportunistic infections, hospital

admissions, etc. In other words, participation in EAPs may lower the overall cost of care for highly treatment-experienced patients.

**Disadvantages of EAPs: Payor Perspective**

The high administrative costs (both for IRBs and for clinical and research staff) are generally not reimbursed. Further, enrollment of patients in EAPs for new drugs establishes an immediate market for drug within the network when the drug is approved by the FDA.

## INDUSTRY PERSPECTIVE

Expanded access programs evolved as a result of the demand from patients and HIV/AIDS activists for access to life-saving medications. They are not a requirement of the drug approval process, but are offered as a means to provide access to life-saving therapies for patients in need prior to approval. Pharmaceutical companies have continued to offer them because they take their responsibility to contribute positively to the treatment of patients with HIV seriously. In turn, it is hoped that the companies may benefit from the collection of critical safety data. In reality, the data collected as part of EAPs rarely provide much useful information for the sponsor.

By design, EAPs differ substantially from Phase 2b/3 studies, which are designed to collect very comprehensive data in highly selected patient populations that can be dissected in multiple ways to answer regulatory questions that arise in the process of approving a drug. An EAP is designed to meet an unmet medical need, upon which is layered the provision of additional safety information from a more broadly representative patient population.

Some have criticized the way that EAPs have evolved, suggesting that they can essentially become a way to bring about an early launch of a new drug, increasing the agent's visibility in the treatment community before marketing approval. It has been argued that this can increase physician comfort with prescribing the drug, resulting in broader and more rapid uptake once the drug is approved. In addition, it has been suggested that theoretically, a large EAP could generate

pressure for state and federal insurance plans to cover a drug once it reaches the market, although there is no published evidence that this is the case.

***Case Study: Darunavir Expanded Access Program***

Tibotec initiated the EAP during the enrollment of the phase 3 program. To date 45 countries have participated in the EAP for darunavir (TMC114), with a few more still to come on line. As of February 1, 2007, there were 894 patients who had participated in the US and more than 2400 in the rest of the world. Tibotec's objective was to provide access to darunavir as broadly as possible for patients in need and to make the EAP available to a wide range of types of sites. In the US, 225 sites initiated the EAP, with 166 sites actually enrolling patients. Approximately 70% of all sites globally who initiated the EAP went on to enroll patients.

Among the sites approached to offer the EAP, approximately 15% decided not to participate, for reasons including:

- Lack of patients needing new drugs
- Lack of 2 active agents to combine with the new drug
- Administrative burden
- Insufficient reimbursement
- Competition for time/resources from clinical trials
- Insufficient time to complete initiation, particularly among academic centers

In the US, the EAP started enrolling in October 2005 through June 2006. The enrollment period is fairly well defined in the US, with enrollments ending upon drug approval and the EAP ending as the drug enters the market. In Europe, the period between the end of enrollment and the rollover to marketed drug can vary widely according to the approval and reimbursement policies of different countries. It is possible in Europe to have patients remain on the EAP for as long as 12 months post approval while a country finalizes its reimbursement policy.

**Challenges from Industry Perspective**

The need for access to experimental agents among salvage patients is clear. However, few data exist to suggest how large that population of patients is. Companies face challenges in trying to understand the scope of the demand for an emerging treatment and planning adequately to manage the supply of drug for the program. The expedited approval process has significantly shortened the time to drug approval. In effect, this results in shorter EAP programs and reduces the incentive for clinicians to want to participate.

Managing communication strategies around EAPs is also a challenge. Patients and providers understandably want as much information as possible, while regulatory agencies have concerns about companies crossing the line between providing information and promoting unapproved products. Companies have often erred on the side of providing too little information about their EAPs.

Recognizing the administrative burden associated with administering an EAP, drug companies strive to simplify the case report forms (CRFs) and other paperwork associated with EAPs. Strategies include requiring standard of care treatment as the protocol, decreasing the amount of additional work required for sites to comply with the EAP protocol. For example, companies try to minimize the need for additional laboratory work that increases the workload and creates additional burden in the form of exemptions. The standard operating procedures of the CROs can contribute to the burden as a result of data collection requirements they place on the participating sites. At issue is the fact that the CROs typically do not differentiate between a standard operating procedure for an EAP and a normal clinical trial. Also, requirements of EAP vary widely among the different programs.

**Data Collection**

Companies recognize the need to find a balance between data collection that becomes too burdensome and the need to collect safety data that may identify emerging safety issues and ultimately help define the best use of the drug. In reality, the data that are collected are not used often. Because of the uncontrolled, noncomparative nature of the data, they have limited value for publication. High rates of serious adverse events are not unexpected in highly treatment-experienced patients who are already on many drugs; identifying whether SAEs (severe adverse

events) relate to the study drug is extremely difficult. A standardized data collection protocol for all EAPs would be highly beneficial, as that would allow data comparison across studies. In addition, while the current EAPs have been coordinated to allow enrollment in more than one program, there is no coordination of data collection. This means that, for a patient enrolled in multiple programs safety data is collected for each program. Is there an opportunity for harmonization of the data collection forms and for harmonization of what data are being collected?

**Reimbursement Issues**

While everyone agrees that substantial work is required of the EAP participating sites, whether and how companies should reimburse for that work is not clear. One issue is that the costs vary widely between academic centers and smaller clinics and private practices. A payment that will cover the expenses of the smaller clinic very likely will not cover the expenses for an academic center. Ideally, individual sites would probably benefit most from a per-patient fee. However, that raises the issue of how much can a company pay without seeming to be paying to promote recruitment of patients for their investigational drug, especially when those patients are likely to continue as paying customers once the drug is approved. As a result, the companies that do offer reimbursement intentionally limit payment to sites. There is little to no guidance on what fees are allowed.

An important aspect of ensuring the clinical benefit of EAPs is trying to ensure is the availability of a second new (or investigational) agent available, which frequently entails collaboration between pharmaceutical companies. This requires a huge effort on the part of the drug companies, but is ultimately of significant benefit for patients in terms of avoiding the risks of virtual monotherapy. Of course, it is only possible when multiple new agents come to market within the same time frame. In addition, legal limitations exist in some European countries regarding the use of more than one investigational agent at the same time unless they are being administered as part of a single clinical trial.

In Europe, standardized guidelines on mechanisms to provide access before a product is approved in the first country are lacking. As a result, many smaller countries have limited

understanding of the objectives of EAPs and the distinction between EAPS and clinical trials. More standardization of legislation around these issues is required.

Ultimately, EAPs are prepared at substantial risk to drug companies, who must invest significant resources in planning EAP implementation long before a drug has completed Phase 2 development. This entails ensuring adequate supply of drug for the protocol (which requires estimating demand 2 to 2.5 years before Phase 2b clinical data are complete), recruiting investigators, drafting the protocol, and increasing staff to support the EAP, all before Phase 2b clinical data are available.

## REGULATORY PERSPECTIVE

From the perspective of the regulatory agencies, the primary concerns are the need to balance the needs of patients for access to new drugs with adequate safety monitoring. The following section presents a brief overview of the issues from the points of view of both the FDA and EMEA.

### ***US Food and Drug Administration***

The FDA has a longstanding history of facilitating access to investigational therapies, going back to cardiovascular drugs such as metotropol and nifedipine in the 1970s. As noted, it was the organization of HIV patients and AIDS activists in the first decade of the HIV epidemic that led to the current approach to expanded access in the US.

The existing regulations that regulate the use of investigational drugs in patients include

- 312.34—treatment use of an investigational new drug
- 312.36—emergency use of an investigational new drug

The Food and Drug Modernization Act (FDAMA Sec. 561) authorized the FDA to enact further regulations about expanded access to experimental therapies. FDAMA first provided for access to experimental therapies for individuals and populations with serious and life-threatening diseases and no satisfactory alternatives.

The standards required an evidentiary basis linked to the size of the population and the seriousness of the disease. They also required sufficient evidence of safety and efficacy to support the use of the drug and a reasonable basis to suggest that the therapy may be effective and would not expose patients to unreasonable and significant risk. In addition, it was specified that such access would not interfere with clinical studies necessary to support marketing approval of the drug.

**FDA's New Proposed Rule**

The FDA has recognized that the current regulations do not reflect how the system actually functions and may promote inequitable access to programs. As a result, on December 11, 2006, the FDA published a proposed new rule on expanded access to investigational drugs for treatment use [8]. The new regulations are designed to improve access to investigational drugs for patients with serious and life-threatening diseases who have no satisfactory alternative therapies.

The new proposed rule follows a few basic principles:

- The goal of expanded access is treatment, not data development.
- The rule describes three different treatment use scenarios based on population size to allow for more rigorous requirements with increasing exposure.
- The evidentiary standard necessary to support use will vary with the size of the population and seriousness of the disease.

In general, the goal of the new rule is to facilitate the availability of promising investigational drugs to seriously ill patients who have no satisfactory alternatives as early in development as possible. It specifies that the potential benefits must justify the potential risks, and that access will not interfere with clinical trials. The routine safeguards that apply to clinical trials are also applicable to EAPs.

For individual patients, the physician must determine that the probable risk from using the drug does not exceed the risks associated with the disease. For its part, the FDA must determine that the potential benefit justifies potential risk, that the risks are not unreasonable, and that the

patient cannot obtain access under another type of IND (e.g., a patient does not meet the requirements for a clinical trial or lives in an area without access to clinical trials). Emergency use can be granted to individual patients.

Additional safeguards are built into the rule, including

- Treatment is limited to one course
- The FDA requires reporting and may require special monitoring
- FDA may request consolidation of cases into single IND (e.g., if there are multiple individual INDs for an agent, the FDA can require the company to roll them over into a single clinical trial)

For an intermediate size population, the requirements state that the access will be provided in cases where the drug is not being developed (e.g., a treatment for a rare disease), or if it is being developed, that the patient is not eligible for clinical trials. Access can also be provided if a drug is approved but withdrawn and available elsewhere (e.g., Europe). In any of these cases, sufficient evidence that the drug is safe at the proposed dose and duration to justify the size of the trial must be presented. Preliminary evidence of effect (either clinical or pharmacological) is also required. Again, additional safeguards have been stipulated:

- An explanation is required regarding why the drug cannot be developed or why patients are not able to enroll in clinical trials
- An annual review to determine whether a treatment IND would be more appropriate is required

The treatment IND or protocol is probably the option that is most applicable to HIV EAPs. This is the situation when a drug is being investigated in clinical trials designed to support marketing, or when trials are complete and the company is actively pursuing marketing approval. Sufficient evidence of safety and efficacy is fundamental. For a serious disease, this would ordinarily consist of data from phase 3 studies or compelling data from phase 2 clinical trials. In the case of an immediately life-threatening disease, there must be a reasonable basis to conclude that the investigational drug may be effective and would not expose patients to an unreasonable and significant risk. Additional safeguards in this situation include a 30-day postsubmission waiting

period before the FDA will decide whether to allow the initiation of the trial, as well as additional monitoring. According to the new rule, treatment IND protocols would have to be listed on the clinicaltrials.gov website.

**The FDA's Involvement in the EAP Process**

The FDA cannot force a company to provide access to investigational drugs for treatment. However, the division encourages the use of EAPs during development meetings with sponsors. They also discuss appropriate timelines for such programs so that they will not interfere with the drug development process.

In HIV, with the recognition of the risks associated with treating patients with only one new drug at a time, the FDA has attempted to encourage companies to study multiple new drugs together and to try to come up with creative study designs that will limit the use of virtual monotherapy and address the evolving therapeutic needs of patients.

The overall goal of these programs is to provide access to investigational drugs for patients who need them rather than to answer safety or efficacy questions. As such the FDA requires limited safety data (e.g., death, serious adverse events). In HIV, the FDA does not require the inclusion of HIV-related serious adverse events and death.

***European Medicines Agency***

According to European HIV guidelines, EAPs are recognized first as a means to provide access to patients who have exhausted existing treatment options and need investigational therapies. In addition, they recognize that EAPs provide an opportunity to supplement the safety database of a drug. However, the need for caution in data interpretation is accepted, recognizing that, by definition, the population in the EAP is heterogeneous, with significant underlying disease. In addition, there is a potential notification bias in that physicians are less inclined to report adverse events in EAPs compared with standard clinical trials.

Recognizing the potential benefits of the data collection made possible by EAPs, the European bias is toward increased data collection, while acknowledging the need for programs that are not

overly burdensome for prescribers and patients. A recurring theme is the need to find a balance between competing interests—the responsibility to provide access to emerging drugs for patients who are in need of them and the opportunity to supplement the developing clinical data and help guide treatment strategies.

However, some Europeans argue quite convincingly that all patients may in fact be best served by more effective use of the data that are available from these treatment-experienced patients and that there is a rationale for finding ways to collect and interpret the data that do not create undue burden for patients and physicians.

The French model, the Temporary Authorization for Use (TAU), offers two possibilities. The nominative TAU (or named patient program) is available for patients on an individual, temporary basis (3 months) on the request and responsibility of the patient's physician. It requires collecting only limited (spontaneously reported) safety and efficacy data. The majority of French patients enroll in cohort TAU, which are designed for groups of patients at the request of a drug company that is well into the approval process for a new drug. The drug can be administered for up to a year with substantial follow-up on safety and efficacy data, collected according to a protocol for therapeutic use

## ROUNDTABLE DISCUSSION

Following the introductory presentations, the meeting was opened up for discussion of the issues identified by the various presenters. Following are highlights of the discussion, organized according to the specific issues. Where appropriate, comments are broken out according to which perspective was being represented.

### CONSENSUS ON THE CURRENT SITUATION

There was broad agreement among all of the groups at the meeting that EAPs provide a societal good by providing access to patients in need. Although solid data on the size of the patient population that is in need of the newest HIV therapies prior to approval is lacking, there is general agreement that some number of those patients do still exist. Despite all the changes in the HIV treatment environment that have occurred in the last 20 years, that need has not gone away—although the need appears to have decreased in that past 5-6 years.

Physicians want to be able to obtain access for their patients, when necessary, to treatments that have not yet achieved full regulatory approval. In addition, both the regulatory agencies (US and abroad) and the pharmaceutical companies recognize this obligation. Although there is a system in place to do this, it is not working as well as it might and may in fact be creating unnecessary barriers for patients and physicians who want access to these treatments.

The tensions that exist in the system are not fundamentally between the groups involved in the process or because of conflicting principles about making access available to patients in need. Instead the tensions emerge in relation to how access should be provided. The issue becomes how to develop mechanisms that will provide access to those in need while maintaining regulatory oversight. Ultimately we are forced to work within the existing structure: e.g., IRBs have their responsibilities, and are not going to grant institutions immunity from oversight.

The roundtable participants agreed that solving the issue of where to go with EAPs should be tied into the changing nature of clinical studies of new agents in general. With the expansion of

the number of available antiretroviral drugs and improvements in efficacy and safety, the entire clinical trial environment in HIV is changing. For example, it is no longer appropriate to be doing studies in which patients are receiving a single new drug unless there is sufficient activity in the background regimen. Compounds considered for EAPs emerge from phase 2a studies with little doubt about their activity—the focus then shifts to the potency of the background regimen and how long-term durability and safety can best be assessed. Moving forward, clinical trials of antiretrovirals should only enroll patients who can construct adequately active regimens, because the real goal of the longer-term follow-up of these studies is to look at long-term safety (e.g., POWER 3 study)

***Issue 1—Defining the need for EAPs***

A fundamental issue is the fact that solid data on the size of the patient population in need of EAP are not available. Not every patient with multi-class resistance needs immediate access to investigational drugs. According to the roundtable participants, the estimates of those patients who are unable to construct an effective salvage regimen range from 1% to 13%:

- According to market research data, approximately 17% of patients on treatment are on their third antiretroviral regimen. Of these, some 6% of patients are unable to construct a viable salvage regimen. This works out to about 1% of patients on treatment who are unable to construct a salvage regimen
- Several of the participants suggested that this number was unrealistically low
- Data from Kaiser Permanente Northern California suggest that about 10% of patients in their system have failed their third (or greater) antiretroviral regimen
- Data from Monogram Biosciences show that among people with viral loads over 100,000 copies/mL, 13% have resistance to three drug classes

Another consideration in terms of defining this population is the urgency of their need for new drugs—in other words, what is the number of patients on failing regimens who are in that category of urgent need of a new drug. Some of the clinicians at the roundtable argued that they don't know of any of their patients who could not wait the 6-9 months until a new drug is approved. Moreover, it was noted that these are often not the patients who are dying—more

commonly the patients dying from HIV/AIDS are those who are not in care at all until they present with advanced disease and opportunistic infections.

Overall, there is an acknowledgment that some of these patients requiring the newest medications offered through the EAPs do exist and there should be a mechanism for providing them with drugs as they become available.

***Issue 2—Tension between EAPs as clinical versus research programs***

*Industry*

From the perspective of industry, EAPs are essentially viewed as a means of providing access to patients in need, not as data-generating protocols—in other words it is primarily a clinical issue. However, at the sites, and from the perspective of the IRBs, they are treated just like any other research protocol.

*Academic Center*

Some academic institutions have a hybrid approach that acknowledges that EAPs provide primarily a clinical function but also recognize that managing an EAP requires the type of expertise found in research departments. In this type of approach, the day to day work of seeing the patients is handled through the clinic, providing an opportunity to bill for those services. Any extra revenue generated there is applied toward the regulatory/administrative costs borne by the research unit.

However, even if an EAP is by definition meeting a clinical need, the fact remains that the drugs are investigational. Even though data may not be prospectively collected with the intention to analyze and publish, these activities are research, and as such require consent.

*Regulatory*

From the regulatory perspective, although recognizing that EAPs create a tremendous burden on the sites, EAPs are designated as investigational by law. Therefore, the requirement for IRB approval and informed consent cannot be bypassed. The only way around that would be through the legislative process. “In effect, from a regulatory perspective, we don’t have any clear way to

discriminate between the clinical and research uses of an investigational drug," noted one regulatory representative.

***Issue 3—Providing access to patients in need, while minimizing the administrative burden***

One question that came up several times during the discussion was whether pharmaceutical companies and/or regulatory agencies can help reduce the burden posed by local IRB requirements. However, it was acknowledged that the IRB system is designed to keep control at the local level, to protect from the potential for abuse on a national scale. Thus, attempts to impose a centralized IRB system will likely not be successful.

From the site perspective, one of the most challenging things about EAPs is that the protocols are all quite different. Might there be a way to standardize them so that some of the administrative work could be lessened?

*Academic Center and Payors' Perspective*

Although companies have tried to streamline the EAP protocols, the conduct of these studies by the CRO is handled like any other normal clinical trial (i.e., in full clinical trial mode). The CROs do not differentiate between an EAP protocol and a standard clinical trial, so that the administrative burden ends up being more or less the same even though the actual data required by the EAP protocol may be substantially less than that stipulated by a clinical trial. This is the reasoning given for the tremendous level of scrutiny and auditing of EAPs by the CRO. The CROs have a single standard by which they are prepared to perform.

It was agreed, however, that CROs are not collecting data that is not requested by the sponsor of the study. Instead, it has more to do with what the CROs consider adequate source documentation. Individual site monitors interpret the requirements to answer specific questions.

One example of the administrative overkill is the requirement, common to EAPs, that the documentation include every patient's entire medical history each time they enroll in an EAP. Given that some of these patients have more than 20 years of treatment history, the copying (and

storing) of those records represents a significant burden for the office staff. For example, is it absolutely necessary to know how many times a patient stopped and started zidovudine in the past 20 years—might it not be sufficient to know that the patient's treatment history includes zidovudine?

***Issue 4—Reimbursement***

The participants agreed that EAP sites should be reimbursed to help cover the costs of administering the EAP protocol. How do we find a funding mechanism to help compensate the clinical sites?

*Industry*

Pharmaceutical companies are concerned that paying per-patient fees might lead to the impression that they are trying to induce the use of their investigational drugs. Companies recognize that EAPs have changed over time and also how much administrative work is involved at the site to manage an EAP protocol. Although some companies are beginning to offer reimbursement, because of the high level of scrutiny that pharmaceutical companies are under, the potential for the perception of financial incentive to enroll patients in EAPs leads them to be very cautious.

From their experience during the development of the darunavir EAP, Tibotec recognized that some 15% of sites were declining to participate due to the administrative burden and lack of reimbursement. In response Tibotec initially offered to provide an upfront fee to help with set up, to get things up and running. Depending on the type of site, it became apparent that an upfront fee might not be sufficient. The per-patient fee was developed in response to the administrative burdens associated with the ongoing management of the SAE reporting that is required by the protocol.

Pfizer is offering per-patient reimbursement for the maraviroc EAP, but has intentionally underfunded them to avoid the perception of financial inducement.

Pharmaceutical companies note that EAPs are extraordinarily expensive propositions—they are offered because it is thought to be the right thing to do from a clinical perspective.

*Academic Center*

One physician-investigator acknowledged his ambivalence about per-patient reimbursement for EAPs, noting that such payments might raise questions if there were an unexpected safety event or other issue that affected the patients enrolled in an EAP protocol.

*Regulatory*

The FDA does not get involved in discussion regarding site reimbursement for EAPs. There are no regulations forbidding it. The issue of per-patient fees is more of a concern for healthcare compliance and the Office of the Inspector General, who looks at reimbursement in terms of how it might be inducing clinicians to use a new drug before it enters the market—to influence prescribing behavior in the future.

## RECOMMENDATIONS FOR MOVING FORWARD

***Issue 1—Defining the need for EAPs***

Developing a better understanding of how large the need for early access actually is will be necessary prior to designing and implementing improvements to the system.

*Academic Site*

Some suggested that the shrinking size of the EAPs is not necessarily a bad thing in that it likely reflects a decline in the population of patients who are in urgent need of the newest therapies offered through the EAPs.

Safety needs to remain a top priority in the design of EAPs. Thus, the apparent trend to loosen the entry requirements for EAPs to include patients of any CD4 cell count or any viral load is a cause for concern to some. Although the drugs that become available through EAPs have established some level of efficacy and safety data, there is still much that we don't know, particularly in terms of drug interactions and the development of drug resistance. From this perspective, we should be careful about using them too widely, and some have argued for more restrictive entry criteria.

Another investigator commented that while there will always be drug resistance, the population of patients who need immediate access to investigational drugs will to continue to shrink. This perspective raises the question of how relevant EAPs will be in the future, if, as is expected a much greater percentage of patients are going to have undetectable viral load. In fact, treatment guidelines are increasingly emphasizing that the goal of therapy for patients at all stages of disease is undetectable viral load. That the guidelines are saying this reflects an assessment of recent clinical trials data and the fact that this treatment goal was achievable. Is the whole question of the need for EAPs going to be much less relevant by the time we're able to make any kind of recommendations? This sparked the suggestion that perhaps we should be moving toward an individual IND model in the US, rather than having large EAPs.

Another view expressed was that the most acute need seen now has little to do with imminent risk of death, but rather the imminent risk of virologic failure due to their unwillingness to continue with enfuvirtide. Although they are not viremic, they are on an intolerable regimen, and yet they can't get into expanded access because they are not viremic.

*Community*

A community representative noted that as a patient he becomes concerned when he hears people saying that maybe EAPs are no longer necessary or that they should be more restrictive. In addition, he expressed concern about those patients who still do not have access to investigational drugs because of where they live or the fact that their clinician is not connected to the system.

As the numbers of treatment-resistant patients keep shrinking, he suggested that we consider the creation of a centralized nonprofit research organization that could help process individual emergency INDs for patients. Ideally, it would be a kind of centralized IRB that is funded by many sources so that there would be no question of conflicts of interest. Academic institutions that are not able to participate in EAPs because of the administrative burden could then refer patients who need access to that organization.

*Regulatory*

The FDA has generally left entry criteria relatively loose on purpose, rather than restricting them. In most cases, EAPs are opened for drugs that are relatively close to approval, so that by the time patients receive an agent through the EAP, a relatively good sense of the efficacy and safety of the drug has been established. In effect, an EAP is a bridging mechanism that provides access in the period 6-9 months before the final approval of the drug.

It was also noted that the criticism that EAPs in particular result in unnecessary drug resistance as a result of virtual monotherapy is somewhat unfair, since clinical practice once the drug is approved probably results in the same thing on an even broader scale. For the most part, clinicians who take the time and effort to participate in EAPs are doing so for patients who genuinely need the drug. In fact, the decreasing size of EAPs in recent years would indicate that

the whole process is somewhat self-limiting, which makes the need for more restrictive criteria somewhat questionable.

***Issue 2—Tension between EAPs as clinical versus research programs***

*Academic center*

One academic investigator commented that it is undoubtedly a positive thing that we have shortened the time to approval of antiretroviral drugs, adding, "Now I think that we have to focus on ways that we can design small studies to look at safety and pharmacokinetic issues—to get the information that we as clinicians need to help us know how to use new drugs as effectively as possible."

*Nursing Perspective*

In many settings the nurses who are administering the EAP are actually clinic nurses and not research nurses, so the time that they spend dealing with the EAP is time that is taken away from patient care. Thus, some type of reimbursement for that time could help reduce the burden on the clinic from participating in the EAP.

*Industry*

One perspective is that – given that patients are taking investigational drugs if they are participating in EAPs -- the potential to gain a better understanding from those patients' experience with the drug should be better utilized. One comment was, "I recognize that we need to balance that with the need to get the drug to patients in need, but we need to look at whether there is another mechanism that would allow patients to access drug while at the same time providing usable data about the use of the drug."

One participant suggested that a possible area where some latitude might be achievable through regulation rather than legislation, is to develop a modified standard for monitoring an EAP that reflects the data collection needs of the EAP rather than the requirements of a phase 1-3 clinical study.

Another suggestion was to develop a new regulatory framework (i.e., product labeling) that would fall somewhere between investigational drug and approved for marketing (e.g., able to designate a drug as approved for expanded access).

*Regulatory*

The representatives of the FDA at the roundtable were somewhat surprised by the difference in EAP experience reported by the physician in private practice and those working at academic centers. They had not realized how much more complicated and burdensome it is for academic centers to participate in EAPs.

One thought from regulatory was that there may be a way to develop two types of protocols: one type for academic centers, which would be an actual research protocol designed to address specific questions leading to approval, and which would be reimbursed in the normal way. Such a protocol could address the types of issues normally studied in phase 4 studies. These could be designed to target underrepresented patient populations. A second type of simplified protocol would be developed for private practices and community clinics.

*Academic Center*

The suggestion of two types of protocols needs to be considered from the perspective of the needs of patients and sponsors. Creating more research-oriented EAP protocols in which the results mattered for approval may result in drug companies once again having an incentive to go to those sites/settings that can enroll patients most quickly without the administrative burden of an academic center.

Similarly, if a study is going to collect coherent data, it would have to be more selective about the characteristics of the patients being enrolled, and then it is moving away from the goal of providing access to patients based primarily on clinical need.

Another issue is that although academic centers do research, they are also providing clinical care. In fact, much of the care that is being provided to indigent patients and other underserved populations is occurring at academic medical centers, because they are the publicly funded

institutions in the major metropolitan areas. The problem is that the people providing the care are not the same people doing research--that is not their mission. But because they are located in an academic center, they are burdened by the entire superstructure that goes with the institution. But the need is still there for the patients and the rationale for having access to these programs for our patients is the same as exists in other settings.

Regarding targeting EAPs for special populations, it was noted that when talking about salvage therapy, we are still at a point in the epidemic where the majority of patients from underserved populations are at an earlier point in the disease, meaning that there are fewer of those patients on salvage regimens. The same centers that are enrolling 40% of their studies with women and minorities are only able to enroll 10% of those patients into salvage studies because the majority of those patients have not reached that point yet.

*Industry*

The idea of having a special EAP clinical trial for academic centers is interesting, but given that we are trying to meet medical need, having a trial for special populations may not really be addressing the medical need. Another concern is that if a trial is designed as a full safety study to offset phase 4 studies, but it starts before the filing, there is a risk that it somehow gets wrapped up into the filing and potentially could slow down the approval process. Additionally, companies are not going to want to be adding another full safety study at the time that the phase 3 studies are coming to completion, and at the same time they are trying to set up the EAP. Company resources are already stretched to the limit at that point.

***Issue 3—Providing access to patients in need, while minimizing the administrative burden***

The panelists agreed that much of the burden associated with the EAPs comes from the way SAEs are reported. Sites are required to fill out numerous event forms and also have to manage the huge volume of event reports that they receive as a study site. Yet for all that work, no one is really monitoring these events in a systematic way. In fact, the way the events are reported, without context (e.g. number of patients at risk), makes interpreting the events virtually impossible for both site investigators and IRBs.

One idea that was discussed was to create a central repository of SAE reports that the IRBs and EAP sites can access. The results could be tabulated so that it would be easier to identify trends, and a significant part of the administrative burden of these protocols could be eliminated. It was suggested that it could be designed as a web-based database that the sponsors and IRB can access at regular intervals.

*Industry*

One approach to lowering the administrative burden would be to standardize EAPs in terms of CRF development and safety reporting. At the same time, Europe and the US should begin to collaborate on standardizing the very complex and variable regulatory requirements for EAPs as much as is possible. For example, one suggestion was to look at the way named patient programs are organized in Europe, as they have significantly less reporting requirements than EAPs in the US.

*Regulatory*

Another idea that came out of the discussion was whether there is any potential for companies to collaborate on the design of EAPs that include more than one investigational drug.

The industry representatives agreed that it was an intriguing idea, but cautioned that it might take so long to agree on a collaborative EAP that by the time it was designed the drugs would be approved. One company representative noted that there are discussions ongoing among companies on how they might collaborate on SAE reporting for patients who are on multiple simultaneous EAPs. In addition, it was suggested that there are opportunities for harmonization in terms of what data are collected and perhaps even how data are collected.

However, he added that collaboration in adverse event reporting is going to be challenging. Each company has its own way of collecting those data, with its own data collection forms, coding systems, etc, that they use for all of their drug development programs. These considerations raise doubts as to the feasibility of achieving harmonization of data collection.

The individual IND and emergency IND designations are not going to be useful for providing access to large numbers of patients. An individual IND does not really reduce the paperwork, since it has to go through the same IRB approval as a standard EAP protocol. Emergency INDs are intended for those rare cases when a patient literally needs access within hours or days, which is unlikely to be the case in HIV.

The FDA noted that this meeting was very timely as the agency is evaluating the potential of providing expanded access to experimental drugs for other diseases. It was suggested that the recommendations and difficulties with expanded access programs to HIV drugs discussed at this meeting be compiled and sent to the FDA docket on “Expanded Access of Investigational Drugs for Treatment Use”.

**TABLE 1.** Summary of published data about antiretroviral expanded access programs in the United States

| Drug | Date | Number of patients |
|---|---|---|
| Zidovudine | 1986-87 | 4804 |
| Didanosine | 1989-91 | 21,198 |
| Zalcitabine | 1990-92 | 6705 |
| Stavudine | 1992-94 | 12,551 |
| Lamivudine | 1993-95 | 29,430 |
| Saquinavir | 1995 | 2200 |
| Indinavir | 1995 | 1500 |
| Nelfinavir | 1996-97 | 3000 |
| Amprenavir | 1998-99 | 2217 |
| Nevirapine | 1996 | 325 |
| Efavirenz | 1997-99 | Not presented |
| Delavirdine | 1996-97 | 1527 |
| Adefovir | 1997 – 1998 | 9000+ |
| Abacavir | 1997 – 1998 | 4519 |
| Tenofovir | 3 – 11/2001 | 14,204 |
| Lopinavir/r | 1999-2000 | 10,343 |
| Atazanavir | 2002-2003 | 8733 |
| Enfuvirtide | 8/2002 – 3/2003 | 3610 |
| Tipranavir | 11/04 – 6/05 | >600 |
| Darunavir | 10/2005 6/2006 | 3-5000 anticipated |

**FIGURE 1.**

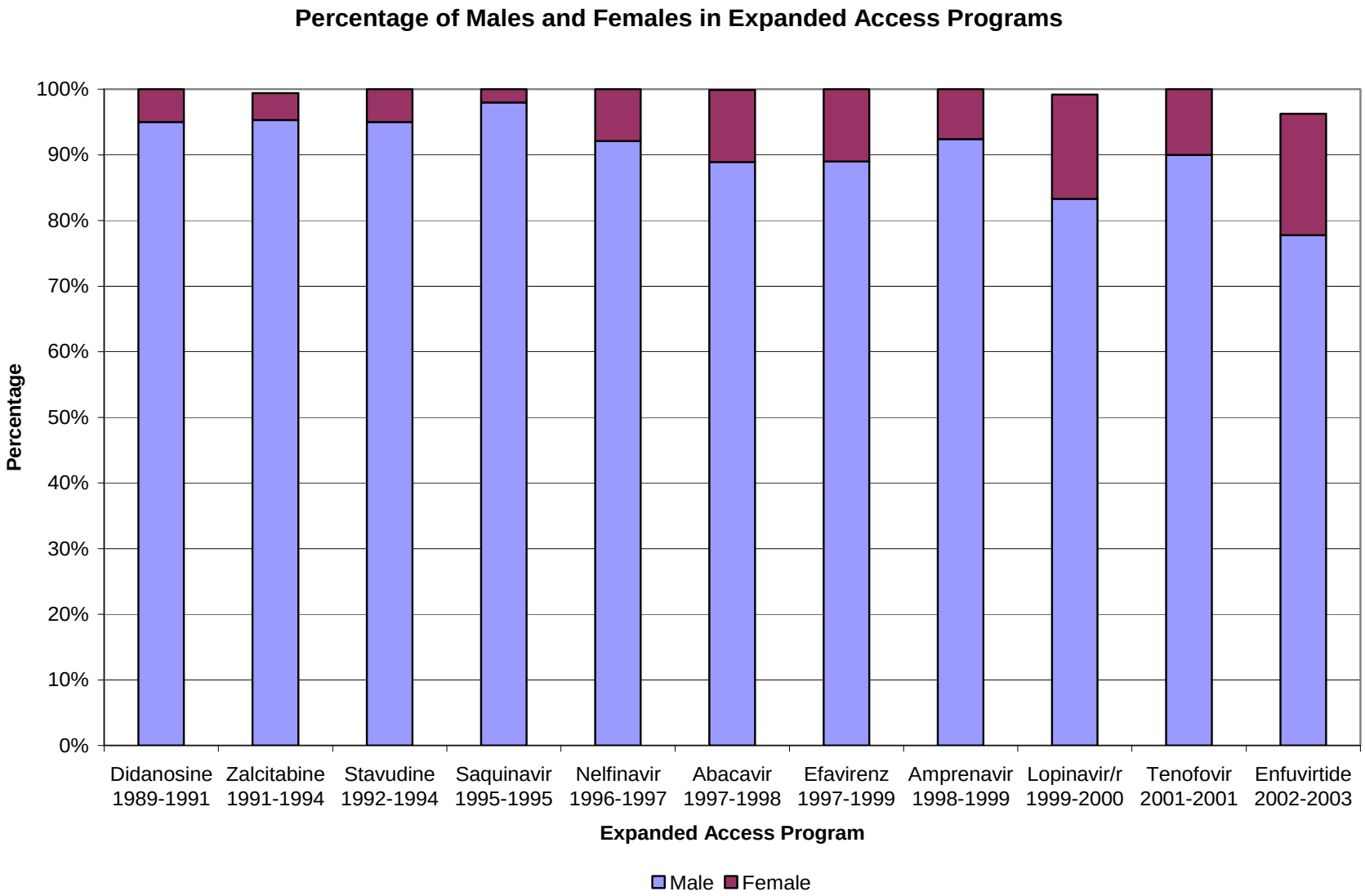

Percentage of Males and Females in Expanded Access Programs
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percentage
Didanosine 1989-1991
Zalcitabine 1991-1994
Stavudine 1992-1994
Saquinavir 1995-1995
Nelfinavir 1996-1997
Abacavir 1997-1998
Efavirenz 1997-1999
Amprenavir 1998-1999
Lopinavir/r 1999-2000
Tenofovir 2001-2001
Enfuvirtide 2002-2003
Expanded Access Program
Male
Female

**FIGURE 2.**

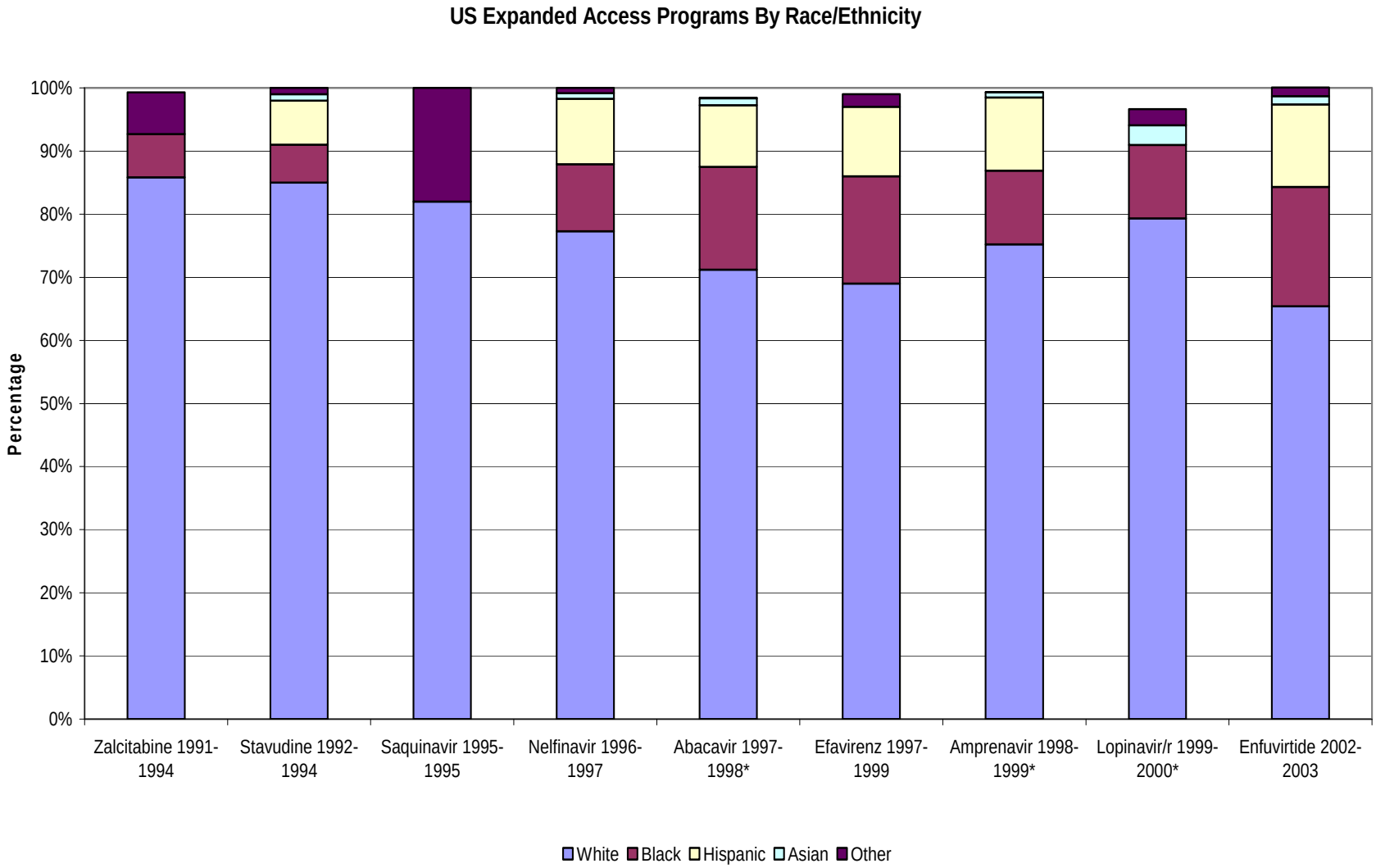
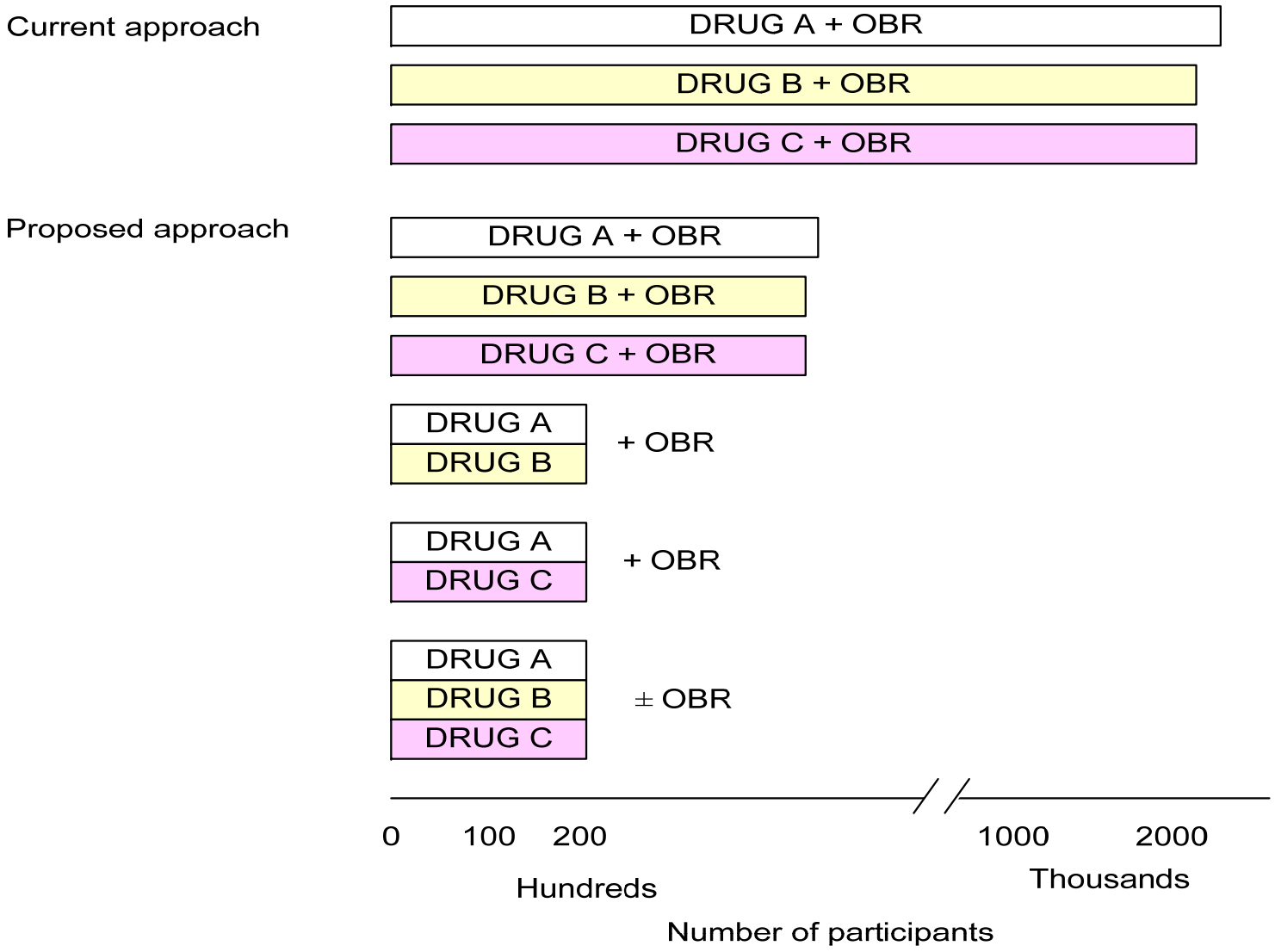

US Expanded Access Programs By Race/Ethnicity
Percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Zalcitabine 1991-1994
Stavudine 1992-1994
Saquinavir 1995-1995
Nelfinavir 1996-1997
Abacavir 1997-1998*
Efavirenz 1997-1999
Amprenavir 1998-1999*
Lopinavir/r 1999-2000*
Enfuvirtide 2002-2003
White
Black
Hispanic
Asian
Other

**FIGURE 3.**


Current approach
DRUG A + OBR
DRUG B + OBR
DRUG C + OBR
Proposed approach
DRUG A + OBR
DRUG B + OBR
DRUG C + OBR
DRUG A
DRUG B
+ OBR
DRUG A
DRUG C
+ OBR
DRUG A
DRUG B
DRUG C
± OBR
0
100
200
1000
2000
Hundreds
Thousands
Number of participants

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