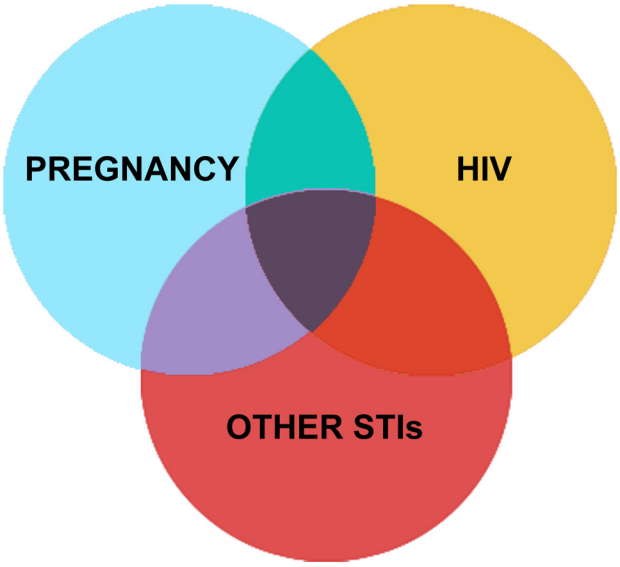
Multipurpose Prevention Technologies *for* Reproductive Health

2011 SYMPOSIUM

Executive Summary

Washington, DC, USA

3-4 November 2011



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The **Initiative for Multipurpose Prevention Technologies (IMPT)** for sexual and reproductive health was established in the spring of 2009 to unite reproductive health researchers, health care providers, policymakers, advocates, product developers, and donors behind a focused objective: to advance the development and introduction of products that can be used in various combinations to address multiple sexual and reproductive health needs, namely unintended pregnancy and STIs, including HIV.

The **mission** of IMPT is to raise awareness about and support for new and existing multipurpose prevention technologies that can be used in various combinations to address multiple sexual and reproductive health needs.

The IMPT's uniqueness is to focus on emerging technologies in combination with technologies that are currently available. While there are not many existing MPTs other than condoms, there are single purpose technologies that can be combined either with each other or with new technologies/drugs and other novel technologies are in development.

Our vision is to advance these promising technologies as quickly and efficiently as possible through an integrated development program from pre-clinical investigation to, clinical testing, regulatory approval, scale-up, public readiness, and product evaluation. The **IMPT** strives to:

1) Mobilize financial, scientific, and political resources to advance the development and access of MPTs;
2) Build synergy and cooperation between scientific disciplines that will help facilitate collaborations and expedite product development and implementation;
3) Develop a cross-disciplinary advocacy strategy and promote increased support for MPTs.

Multipurpose prevention technologies (MPTs) for sexual and reproductive health, also referred to as "combinations" or "dual" technologies include vaccines, microbicides and devices (e.g ., intravaginal rings, diaphragms, etc) and are designed to address multiple sexual and reproductive health needs, including prevention of unintended pregnancy; prevention of sexually transmitted infections (STIs), including HIV; and/or prevention of other reproductive tract infections (RTIs), such as bacterial vaginosis or urinary tract infections. **MPTs** that are acceptable, affordable, and widely available would greatly improve health and save resources across the globe.

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It was made possible by the generous support of the American people through the United States Agency for International Development (USAID) under terms of the Cooperative Agreement # GPO-A-00-06-00005-00, the Mary Wohlford Foundation and the Population Council.

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An electronic version of this document is available at http://www.cami-health.org/2011-symposium/index.php. Other organizations that support the Initiative can post this document on their websites as well. For questions or comments, please contact: cami@cami-health.org

Executive Summary

Background: The consequences of unintended pregnancy, HIV, and other sexually transmitted infections (STIs) are among the great public health challenges of our time; women worldwide bear substantial social, health and economic burdens of unintended pregnancy and STIs. The Initiative on Multipurpose Prevention Technologies (IMPT) convened a Symposium in November 2011 to advance the agenda for technologies that could simultaneously address multiple sexual and reproductive health (SRH) needs. The Symposium brought together experts to discuss and advance the emerging science of MPTs, and to outline steps to ensure that these products are safe, cost effective, accessible and acceptable to the end user. The symposium provided a critical opportunity for researchers, advocates, donors, and other key constituents to take stock of progress on MPTs and look ahead to consolidate these gains as research continues.

Target Product Profiles: A number of previous discussions focused on identifying existing and emerging scientific approaches that could be applied to developing MPTs. They concluded that developing MPTs is challenging but feasible, and proposed a framework for MPT development to help assess and prioritize candidate products according to their development potential, likely impact, and market potential. Working groups formed to develop target product profiles (TPPs) for drug-drug, drug-device, and multipurpose vaccine combinations. The interplay among different attributes is complex and varies among product concepts, but general priority indications and formulations include: contraception and HIV; contraception and HSV; and long-acting reversible formulations like injectables and vaginal rings. This general approach is consistent with the Bill and Melinda Gates Foundation Dual Protection Strategy, which has prioritized contraception and HIV prevention through injectables or rings.

Incorporating Diverse Perspectives: Successful MPT development needs to both reflect and incorporate diverse perspectives of end-users, providers, regulators, donors and developers. Such products can help policymakers meet multiple health and development goals, which can foster political champions essential for public and private investment. Product development should be also informed by eventual introduction and roll out, which in turn can draw on experience with a range existing products and technologies.

Recommendations

The Symposium generated a number of recommendations related to developing and implementing MPTs in order to advance the field quickly and efficiently:

- **Target Product Profiles (TPPs).** Defining Target Product Profiles (TPPs) based on the most relevant MPT product attributes and parameters is essential, both to prioritize donor investments and to guide developer strategies. This process must be dynamic and regularly informed by emerging data, with the resulting TPPs specifically linked to regulatory pathways. MPT development should continue to pursue methods that use hormonal, non-hormonal and barrier contraceptive approaches to provide more options for women.

- **Pipeline.** A sufficient, sustainable pipeline of MPT scientific concepts and product approaches is needed and should include a range of approaches to allow for more product choice, flexibility in adapting and prioritizing products in response to new data, and greater responsiveness to women's needs. Potential regulatory pathways should be mapped for those MPT products that are furthest along in development.
- **MPT Vaccines.** MPT vaccine development can build on the history of successful multipurpose vaccines developed to prevent other diseases. Meaningful investment in the fundamental science associated with MPT vaccine approaches will be required to move this area of research forward.
- **Hormonal Contraception.** MPT development must continue to be informed by evidence around the interface between hormonal contraception and HIV and work to support the WHO guidance process and the development of a research agenda to further understand this interaction. MPT development should also continue efforts to include non-hormonal contraceptive approaches.
- **Acceptability and Use.** Product acceptability, potential for adherence, and eventual implementation must play a central role in MPT product design and development and should factor into the TPPs.
- **Regulatory Approaches.** Regulatory approaches should form a key component of TPPs, and should be mapped for those MPT products furthest along in development. The IMPT should also identify opportunities to engage regulatory authorities from diverse settings on MPT concepts and approaches, and so their perspectives can inform regulatory strategies for emerging products.
- **"Multipurpose Visits".** To provide critical services to meet current needs while new products are being developed, the IMPT and its allies can work to encourage "multipurpose visits" to provide women with ways to address the dual risks of unintended pregnancy and unwanted infection.
- **Diversity of "Users".** Successful development and implementation of MPT products will depend on a broad definition of 'users' to better understand and address the barriers and enabling factors that will affect product uptake and use within all relevant environments: policy, health systems, and end users.
- **Metrics for "Success".** New health products or innovations generally require a long time to become established, so it will be important to identify realistic metrics for "success" for new MPTs. These should include: 1) developing new approaches to allow for more realistic demand forecasts and more accurate linking of supply and demand, 2) an investment framework for introduction, and 3) strategies for ensuring adequate funding for introduction and roll-out.
- **Funding.** For the MPT pipeline to grow and advance, it will be crucial for donor agencies to maintain current levels of funding and increase those as budgets allow. The field will also need to explore new sources of funding and investment.

- **Advocacy.** The IMPT should work to expand the constituency for MPTs to form a cadre of new advocates in new sectors, and to advance the scientific and product development agendas.
- **Regional Constituencies.** Regional efforts to highlight and build strong constituencies for MPTs should explore establishing national MPT teams involving potential end users, community opinion makers and service providers.
- **Partnering.** MPT developers and advocates will need to seek and create innovative partnerships that bridge the for-profit sector and needs in low-resource countries with poorer populations

Looking Ahead

As work on MPTs advances, efforts to date, recent developments in reproductive health research, and the current economic climate signal three areas for priority emphasis:

- The MPT products currently in clinical testing are heavily dependent on a few combination products, which may or may not prove sufficiently safe and/or effective. Continued, timely funding for the advancement of these "first-generation" products will be essential to informing the potential of such strategies and to setting the stage for sound, strategic pipeline management and funding going forward.
- The IMPT's efforts to map the product should continue and diversify as the basis for fostering a full, frank, and well-informed understanding of the preclinical pipeline, its potential, and what fresh concepts might appropriately be drawn in to enrich and bolster it. Energy and craft are needed—and soon—to identify, analyze, and attract potential additions and creative approaches.
- After a decade of turmoil, there is much more real dialogue and collective support for HIV prevention research, for truly integrated reproductive health services, and for strategic, collaborative review and funding. These heartening and timely developments merit continuation and expansion to meet current economic and political challenges. This means that donors must keep talking, sharing, and seeking synergistic intellectual and financial engagement.

Developing a robust, diverse and sustainable pipeline for MPTs will require sustained and new resources – ideas and people, as well as funding. Opportunities for scientific exchange, innovative thinking and recruiting a range of new talent will build on existing approaches in new ways and attract fresh ideas and solutions. The IMPT is committed to continuing to this work, with long-time and a growing cadre of new partners that will offer the best chance of making these urgently needed technologies become reality.

Background: The Case for MPTs

The consequences of unintended pregnancy, HIV, and other sexually transmitted infections (STIs) are among the great public health challenges of our time. Every day, over 1,000 women die from preventable causes related to pregnancy and childbirth.[1] Some 215 million women experience unmet need for family planning, compromising their health and economic prospects. This unmet need for family planning also contributes to rapid population growth; during the week of the Symposium the world marked the arrival of its 7 billionth inhabitant.[2] While specific manifestations and needs vary by region, women worldwide bear substantial social, health and economic burdens of unintended pregnancy and STIs.

Despite clear biological, behavioral and physiological linkages between the risk for unintended pregnancy and STIs, research in these interconnected aspects of sexual and reproductive health (SRH) often occurs in "silos," due to separate funding streams, diverse scientific expertise, and limited opportunities for dialogue and information exchange. The Initiative for Multipurpose Prevention Technologies (IMPT) is dedicated to bringing together researchers, health care providers, policymakers, advocates, product developers and donors in SRH to develop multipurpose prevention technologies (MPTs) to protect women against unintended pregnancy, STIs, and reproductive tract infections (RTIs).

Meeting Overview

The IMPT was started to raise awareness about and support for the development of MPTs that can simultaneously address multiple SRH needs, specifically unintended pregnancy, HIV and other STIs, and RTIs. The Coalition Advancing Multipurpose Innovations (CAMI) serves as IMPT Secretariat. To advance its agenda, the IMPT convened a Symposium, "Multipurpose Prevention Technologies for Reproductive Health," November 3-4, 2011 in Washington, DC. The Symposium brought together SRH experts to discuss and advance the emerging science of MPTs, and to outline steps to ensure that these products are safe, cost effective, accessible and acceptable to the end user. Through a series of presentations, panels and discussions, nearly 130 participants discussed a variety of considerations for MPTs, including the public health rationale for MPTs in different regions of the world, scientific approaches and product leads, socio-behavioral issues, preparing for introduction, strategies for building constituencies and political will, and the perspectives of product developers, donors, and regulators on advancing MPTs. This report highlights some of the key issues and recommendations that emerged from presentations and discussions. (More detail from the presentations is available at www.cami-health.org/2011-symposium/presentations.php.

The MPT 2011 Symposium was one in a series of meetings being convened by the IMPT to advance MPTs for reproductive health. The first was the USAID sponsored 'Advancing

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[1] WHO. Maternal mortality. http://www.who.int/mediacentre/factsheets/fs348/en/index.html. Accessed November 2011.

[2] USAID. The World at 7 Billion. http://www.usaid.gov/our_work/global_health/pop/news/wpd11.html. Accessed November 2011.

Prevention Technologies Symposium' held in Berkeley, California in 2009, the focus of which was to address the opportunities and challenges inherent in the development of MPTs. The symposium convened a multidisciplinary cadre of 150 participants from 11 countries with expertise in product development, advocacy, engineering, behavioral science and clinical care. An outcome of the Berkeley symposium was the commitment among the organizers and key partners to form an Initiative for Multipurpose Prevention Technologies (IMPT) for reproductive health. The IMPT founders agreed that the initiative should be housed within an organization that could serve as a non-aligned convener and does not have an MPT candidate in development. CAMI was a lead organizer of the Berkeley symposium and was initially created as a non-aligned convener for the California-based California Microbicides Initiative. As such, IMPT founders felt it appropriate for CAMI to serve as Secretariat to IMPT.

The February 2011 meeting on Regulatory Nomenclature related to MPTs involved nearly 25 experts in SRH research, product development and regulatory approval. This was followed by the May 2011 "Think Tank" where some 30 scientists assessed the scientific feasibility of developing MPTs, reaching consensus that developing safe and effective MPTs is scientifically feasible, although challenging. Participants in the May 2011 Think Tank proposed developing Target Product Profiles (TPPs) to inform and focus product development efforts. MPTs will be highlighted in an Opening Plenary presentation as well as a panel session at the International Family Planning Conference in Dakar, Senegal, November 29 – December 2, 2011. In January 2012, with support from the Wellcome Trust, the IMPT will convene a subsequent meeting in London with stakeholders primarily from regions with the greatest unmet need for MPTs, Africa and Asia, to increase support for MPTs and better understand the needs of the end users in these regions.

The MPT Product Development Roadmap So Far

The May 2011 Think Tank was designed to advance the scientific and product development agenda related to MPTs. Discussions focused on identifying existing and emerging scientific approaches that could be brought to bear on developing MPTs. After detailed examination and debate, participants concluded that developing MPTs is challenging but feasible. Given the numerous combinations of targets, active pharmaceutical ingredients (APIs) and devices possible for MPTs, the Think Tank experts further recommended that the IMPT could benefit from a framework for MPT development to help assess and prioritize candidate products according to their development potential, likely impact, and market potential.

The Think Tank recommended that the IMPT develop TPPs to help define and focus its work. (the full report of the Think Tank is available at: www.cami-health.org/documents/050511-MPT-ThinkTank.pdf) Two working groups were formed to examine (1) Drug-Drug and Drug-Device combinations; and (2) Multipurpose Vaccines. Each working group assessed scientific approaches and potential products, and interviewed a number of key stakeholders to determine the most critical product characteristics. The chairs of those two groups presented the following highlights of this process and their initial findings at the November Symposium.

Drug-Drug / Drug-Device Working Group

This group worked to prioritize numerous parameters: indication; routes of administration and dosage forms; and product attributes and parameters (such as packaging, shelf life, and storage conditions). While it was challenging to identify clear product parameters among so many criteria and diverse respondents, priorities in each category did emerge:

- *Indication*: HIV/contraception was the highest priority, followed closely by HIV/and Herpes simplex virus (HSV). Other STIs were generally prioritized in terms of their relevance to HIV, the technical feasibility of product development, the prevalence and treatability of the condition, and its pubic health burden.
- *Dosage Forms*: The major determining factor is product adherence, with vaginal rings identified as the highest priority given that they balance adherence, reversibility and burden on the health system, and may help mitigate some of the side effects associated with systemic exposure.
- *Product attributes:* Most specific attributes were identified within the context of safety, efficacy, and other factors, with a relatively long shelf-life (36 months) and high storage temperature (40 C) as priorities.
- *Efficacy Targets*: For HIV, a minimum of 40-50% reduction in risk, and preferably at least 80% with perfect use and 60% with typical use; contraception should be as highly effective as currently available products; and a minimum of at least 40% efficacy against other STIs.
- *Side effects*: Would need to be determined within the context of safety and efficacy, but in general should be "no worse than individual indication products" such as currently-available contraceptives.

The interplay among different attributes is complex and unique for each product concept and design, making it difficult to define broadly applicable attributes and parameters for all drug-drug and drug-device MPT products. However, identifying general development priorities and fundamental design targets for MPT products is possible, and will help to inform funders as they prioritize their investments, and developers as they focus their research and development efforts.

Multipurpose Reproductive Health Vaccines

The MPT Vaccine Working Group developed their target product profile based on a number of factors: indication, target population, product presentation or delivery mode, action required by user, boost schedule, typical use efficacy, side effect profile, additional benefits, shelf life, storage needs, price, and infrastructure required to store and deliver it. The group solicited concepts for multipurpose reproductive health vaccines, and for each of the ten concepts submitted identified what would be optimally preferred across each of the factors listed above (see www.cami-health.org/documents/MPT2011-pdfs/Panel 1. Whaley.pdf for slides summarizing the ten concepts being developed). The working group drew on these concepts and factors to develop a consensus target product profile with the following optimally preferred parameters:

Consensus Target Product Profile

Parameter	Optimally Preferred
Indication and Mechanism	HSV, HIV, HPV Systemic and mucosal protective concentrations of neutralizing antibodies (and cell mediated immunity)
Target Population	Women/girls; Developed and developing regions
Immunogen, Adjuvant, and Delivery Mode	Well-characterized immunogens (but range of adjuvants and delivery modes)
User-action	Pharmacy or self-administered boosts
Boost Schedule	Mucosal boost schedule uncertain
Typical Use efficacy	HSV (70-90%); HIV (70-90%); HPV (>95%)
Side effect profile	Minimal
Additional Benefits	Important
Shelf life	Years
Storage needs	No cold chain required
Price	$1/dose
Infrastructure	Pharmacy

The working group concluded that multipurpose reproductive health vaccines are technically feasible and should be a goal based on the historical preferences of end-users and providers for combination vaccines, as evidenced in many combination pediatric vaccines. However, the timing for developing multipurpose reproductive health vaccines still needs to be determined. While it may be possible to develop separate STI vaccines, the IMPT supports efforts to determine when it may be appropriate and feasible to initiate combination studies in parallel.

Bill and Melinda Gates Foundation Dual Protection Initiative

The Bill and Melinda Gates Foundation (BMGF) is developing a "dual protection" strategy that focuses on contraception plus HIV prevention. The dual protection investment strategy will emphasize adding HIV prevention to existing contraceptive technologies, although the foundation will make some investment in new dual protection technologies that are still in early stages of development. After reviewing the product pipeline, including the IMPT database, the BMGF has prioritized two approaches: co-administered injectables and the vaginal ring.

- **Injectables**: Injections are highly acceptable methods for delivering therapies and vaccines, and injectables are the most widely used contraceptives in sub-Saharan Africa. Co-administration of two injections to prevent pregnancy and HIV acquisition will likely require little incremental development cost beyond the

investment already being made in efforts to develop injectable HIV prevention (by the BMGF as well as others).

- **Rings:** Dual protection rings can potentially build on the dapivirine ring developed by IPM and slated to begin efficacy trials in 2012. Consistent with the IMPT TPPs described above, the ring may address concerns about adherence, but since it is still a new product concept in sub-Saharan Africa the actual uptake is difficult to predict. It is also still to be determined which contraceptive approach would be best suited to a hormonal contraceptive (HC)/HIV ring: continuous use of a progestin+estrogen ring (thereby eliminating the withdrawal period to provide continuous HIV protection), or a progestin-only ring.

This BMGF initiative will also explore whether providing dual protection can improve cost effectiveness through more effectively identifying target user groups that improves uptake and adherence; the obstacles and opportunities for providing HIV and pregnancy prevention together; and how to better market vaginal products to women at high risk of HIV. Given that they are working toward similar goals, the Gates Foundation and IMPT have been sharing information and collaborating on select activities, such as developing the Target Product Profiles.

Discussion

Symposium participants raised several issues that the working groups and the IMPT should consider as efforts to define TPPs and identify MPTs move forward:

- It will be important to balance the focus on the TPPs with a more open approach that still allows for "serendipitous" scientific advances and discoveries. Specific strategies should focus on accelerating the development of MPTs that could be available in the near term, while the field simultaneously seeks out and fosters newer research ideas and approaches that could feed into longer-term possibilities.
- The MPT vaccine concepts presented are promising and intriguing, but a number of participants noted that at this time they remain fairly aspirational. The "Decade of Vaccines" offers an opportunity to highlight the importance of MPT vaccines. Developers also need to think carefully about the timing of risk when working toward combination vaccines. For example, HPV and HSV vaccines would need to be administered at a young age, so it may not make sense to combine them with contraception.
- MPTs offer the potential to support the integration of HIV, STI and family planning services, long a goal of the reproductive health field. A number of participants noted that, overall, the global public health community has fallen short in its efforts to integrate RH and HIV services; however, others maintained that important progress has been made that can be built upon. Service delivery considerations, such as frequency of HIV testing for ARV-based products and level of skilled provider, will be important aspects to consider in the introduction of candidate MPTs.
- Any MPT will need to be commercially viable over the long term. Engaging the private sector is important but complex, given the perceived risks and uncertain

profit potential of reproductive health prevention technologies. Some of this may be mitigated with combination products that target those STIs common in developed world markets, such as HSV-2, HPV and bacterial vaginosis. Given the overall hesitance of large pharmaceutical companies to work in this arena, smaller companies may be more promising partners and should be sought out for collaboration.

Hormonal Contraception and HIV Acquisition

Concern about the associations between hormonal contraception (HC) and HIV resurfaced with the October 2011 publication of data from the Partners PrEP trial, which suggested that hormonal contraception increased the risk of HIV acquisition in women, as well as the risk that HIV-positive women would transmit the infection to their male partners[3]. Many of the MPT concepts being developed incorporate HC, so any association could have an impact on MPT development. A review of the evidence on HC and HIV focused on the effect of HC use on HIV acquisition. Several speakers then presented their perspectives on this complex issue, proposing priorities for additional research, and exploring its potential implications for MPT development.

A review of studies on HC use and HIV acquisition shows that findings are inconsistent and the available evidence has many limitations. To date, all studies on this potential association are observational, and thus, vulnerable to confounding. Few of the available studies were designed to directly assess the association between HC and HIV, and the quality of information collected on HIV exposure, contraceptive use, risk behaviors, condom use, and other key factors varies widely. Some studies report no significant effect of HC use on HIV acquisition, while others report a harmful effect. The bulk of concern focuses on injectable contraception, with less concern focused on oral contraceptive pills, but evidence is limited on other hormonal methods. Studies suggesting increased risk of HIV acquisition are of mixed quality, but do include some of those studies considered to be methodologically stronger, including the recent data from the Partners PrEP study. However, even among high quality studies, concerns remain regarding the potential for residual confounding. Questions regarding the potential effect of pregnancy on HIV acquisition and progression, as well as competing risks of unintended pregnancy, maternal mortality, and mother-to-child HIV transmission must also be considered.

The international health community has responded quickly in an effort to address the uncertainty prompted by the most recent publication. WHO is convening a technical consultation in January 2012 to determine whether current recommendations on contraceptive use for women at risk of HIV or living with HIV remain consistent with the current body of evidence. The consultation will consider three key issues related to HIV and HC use: 1) potential effects of HC on the risk of HIV-negative women acquiring HIV; 2) potential effects on acceleration of HIV disease progression among women who use HC; and 3) potential effects of HC on risk of an HIV-positive woman transmitting HIV to her male

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[3] Heffron R, Donnell D et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *The Lancet Infectious Diseases* 12(1): 19 – 26. (published online 04 October 2011 doi:10.1016/S1473-3099(11)70247)

partner. Experts at WHO, CDC and USAID are conducting three updated systematic reviews of these bodies of evidence. Given the keen interest and potential urgency of any new recommendation, WHO will work to convey any new information quickly and in a manner that is actionable, including updated provider tools and user information if needed.

Panelists and participants at the November Symposium highlighted a number of priority questions and key considerations related to HC, HIV and the implications for MPT development.

- Both clinical and basic research is urgently needed to confirm or refute the HIV/HC association. [NB: The Bill and Melinda Gates Foundation convened a technical meeting in December 2011 to discuss priorities in future research, including whether a randomized controlled trial is warranted and feasible; what kinds of data could be collected in other studies to help address these questions; and what is needed to better understand the physiological response to specific hormones.]
- A number of organizations have projects underway or being planned on related questions, for example:
    - Researchers at CAPRISA will be undertaking several studies and analyses to study changes in the biological interactions between female sex hormones and inflammation in the female genital tract associated with HIV-1 acquisition in young women (see website/slides for more details).
    - FHI 360 is conducting an analysis of individual records drawing on a wide range of clinical trials.
    - The Rakai Health Sciences Program, in collaboration with Johns Hopkins, is conducting an analysis among serodiscordant couples to assess whether HC impacts HIV acquisition in women or HIV transmission for HIV-infected women to HIV-uninfected men, restricted to couples who do not report use of condoms, in order to address concerns about confounding by differences in self-reported condom use.
- More evidence is needed on the relationship of specific progestins with HIV, and this evidence then needs to be urgently translated into policy and practice. Given the widespread use of Depo-Provera or Depot medroxyprogesterone acetate (DMPA) in countries with a high burden of HIV, understanding the mechanisms through which DMPA use might facilitate HIV acquisition are critical to inform interventions that balance the desire to control fertility with HIV risk reduction.
- In many settings there is de facto little contraceptive choice or method mix. Restricted contraceptive choice underscores the need for a broader method mix, especially one that includes long acting reversible methods; however, due to limited evidence, the relationship between other methods (such as contraceptive implants, patches, rings, or hormonal or non-hormonal IUDs) and HIV risk is unknown.
- Symposium participants overall felt that there was no reason for MPT development or efforts to "wait" or shift, although several noted that concerns about HC and HIV underscore the need for MPT development to also emphasize and invest in barrier and non-hormonal methods.

- For the time being, women and couples must continue to be counseled on all contraceptive methods and on dual protection to prevent both unintended pregnancy and disease transmission.
- The MPT field anticipates with keen interest the deliberations and outcomes of the January 2012 WHO technical consultation which will have immediate implications for policies and practice, in addition to influencing work on MPTs.

Product Developer Perspectives

Currently MPT product development is undertaken primarily in the academic and not-for-profit sectors. Representatives of several of these organizations and small companies were invited to offer their perspectives on key challenges and opportunities for developing MPTs. Among the many issues raised, the panelists and Symposium participants highlighted the following:

- The "pipeline" of MPT products currently relies heavily on combining anti-retroviral drugs and hormonal contraceptives, and there is some concern that the portfolio is not sufficiently balanced in terms of risk and strategy. For the near and medium term, the choices about what active agents can be used for MPTs are fairly limited. At present one ARV, tenofovir, has proof of concept [4] as a topical agent and another, dapivirine, will enter clinical efficacy testing in rings in 2012. While there is some real momentum and opportunity, relying so heavily on ARVs and HC presents a risk for MPT development.
- One participant noted that MPT development at present is more of a collection of ideas and approaches than a traditional product development pipeline. The IMPT's pipeline review has identified some promising emerging approaches. At the same time, this review has underscored that the field needs to actively look for new approaches and concepts to diversify this pipeline, in particular safe and effective alternatives to contraceptive hormones which have been in use for more than 50 years.
- Topical use of hormones (such as in a vaginal ring) introduces a degree of uncertainty in terms of any association with HIV and other STIs. Evidence on the interaction between HC and STI acquisition or transmission to date has come from injectables or oral contraceptives, and topical use may have quite different effects. Safety of administering hormones vaginally is a research focus for MPT development, and this work will continue and expand.
- As products move through the pipeline it is important to define and understand more specifically the target user groups so that user needs and preferences will be factored into product development and positioning.

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[4] This was based on the 2010 results from the CAPRISA 004 trial which showed that, in women who were instructed to apply tenofovir gel before and after sex , the risk of HIV acquisition was reduced by 39% overall compared to women on placebo gel. The Symposium took place in early November 2011, just prior to the gel arms of the NIH/MTN VOICE trial being stopped because there was no evidence of effect in reducing the risk of HIV acquisition. In the VOICE trial, women were asked to insert the gel every day whether or not they expected to engage in sex. A confirmation trial (FACTS 001), designed to replicate the CAPRISA 004 protocol, has begun enrolling 2,600 HIV-women, 18-30 yrs of age, at nine sites in South Africa. Results are expected in early 2014.

- Combining APIs by definition makes product development more complex. The challenges of identifying appropriate biomarkers and surrogates for STIs and contraception will be compounded when trying to measure multiple effects. Regulatory processes will be similarly complex, and developers may face challenges in piloting MPTs through regulatory channels (see below). Finally, defining a market for any new product category is often riddled with uncertainty, and defining a market for MPTs may be even more complex.
- As products move into clinical testing, it is important to define the economic model. MPTs could incorporate complementary technologies that have commercial potential for different indications, populations and settings. For example, Merck enjoys a $600 million/year market for its contraceptive vaginal ring. Rings or other technologies could be developed for other indications prevalent in the US and Europe such as HSV, incontinence, or menopausal symptoms. Such an approach could be leveraged to subsidize sustainable, lower cost products for other indications for low resource settings.

Regulatory Perspectives

MPTs present unique challenges for regulation. MPTs may not fit into discrete regulatory categories of *drug, device*, or *biologics,* though they may involve any – or any combination – of these. Addressing different indications may involve more than one department of a regulatory agency, such as antivirals or contraception. Existing regulatory guidance may not be applicable to some MPTs. Recognizing this challenge, the IMPT includes a specific area of work, led by the Population Council, that focuses on facilitating regulatory pathways for eventual MPT approval. This work emphasizes clarifying existing guidance and laying out a series of questions for regulators to pave the way for regulatory approval of drugs or devices that address multiple indications. Panelists were asked to reflect on the regulatory processes and prospects for MPTs; given the composition of the panel and the fact that much of the R&D is occurring in the USA, much of this discussion centered on the FDA processes.

- Within the FDA, MPTs could enter the licensure process via several different routes. For MPTs, the Center for Drug Evaluation and Research (CDER) would consider drugs, the Center for Biologic Evaluation and Research (CBER) would review vaccines, and the Center for Devices and Radiological Health (CDRH) would consider barrier methods and other devices. The FDA also has an Office of Combination Products (OCP) that determines where the application will be reviewed in cases where the primary mode of action is not obvious or easily determined.
- Generally, for a product with more than one drug substance or drug product, the sponsor is required to develop a rationale for each substance or product.
- The FDA has mechanisms for expedited review and, depending on the indication that is being pursued, it may be possible to request expedited review for some MPTs.
- The FDA traditionally requires a randomized controlled Phase 3 trial, but recognizes that sometimes this is not feasible. For example, it has approved vaccines based on

immune response. The FDA remains willing to consider surrogate endpoints for MPTs when the scientific process moves forward sufficiently in identifying them.

- Once a drug, device or vaccine is licensed for one indication, obtaining licensure for a different or supplemental indication is common. A recent example is the HPV vaccine, which was initially approved against HPV, then later for genital warts and again for anal dysplasia.
- The European Medicines Agency's (EMA)"Article 58" mechanism allows the EMA, in collaboration with WHO, to convene an expert panel to provide a scientific opinion on products intended for markets outside the European Union. Scientists and/or regulators from developing countries can be invited to participate in this process. The International Partnership for Microbicides (IPM) has worked with the EMA through Article 58 with the dapivirine ring, and this process may prove an appropriate regulatory approach for MPTs.
- The State Food and Drug Administration of the People's Republic of China (PRC) closely mirrors the US FDA with a similar structure and review processes. While there was no official representative from the PRC FDA at the Symposium, researchers anticipate that it will likely be interested in the US FDA's approach to MPTs overall, as well as its review of specific candidate products.
- The IMPT will continue to explore regulatory approaches and pathways relevant to MPTs. Representatives from a number of regulatory agencies will participate in the London consultation in January 2012, providing an opportunity to hear additional regulatory perspectives on MPTs and incorporate them into development approaches.

Introduction of the First MPT: Lessons Learned to Facilitate Access

Planning for access is critical to ensuring that the promise of new technologies translates into real public health impact. As science moves forward with developing and testing MPTs, parallel efforts must prepare to introduce and disseminate these products. Product introduction and delivery is complex and challenging, and will require substantial and sustained investment. Several panelists were invited to reflect on both the successes and failures of other technology introduction efforts to inform planning for and eventually introducing MPTs, particularly in resource limited settings.

- Numerous frameworks for strategic technology introduction have been developed by international health agencies, including the female condom, emergency contraception, and other RH technologies closely related to MPTs. Any document outlining a strategic approach to MPT introduction should only be developed after a thorough analysis of existing introduction strategies, with a strong case being made for any new framework.
- Providers and provider bias can play a critical role in determining real "access" to technologies, and should be addressed as a critical component of any technology introduction effort.
- Ensuring access to technologies and services goes well beyond "technical" considerations, such as training, supply chain and service availability. Power

dimensions in intimate partnerships, education and economics underlie women's ability to make choices about technology use and to act on these decisions.

- Traditional categories associated with contraception such as "provider dependent" or "user dependent" may be blurred for some MPTs in development. For example, ARV-containing gels or rings will likely require prescription and monitoring by a provider, with active use being user-dependent.
- Product adherence is a major concern. Although pericoital methods can present challenges for adherence, many users do prefer them. Long-acting, provider-dependent technologies such as implants can improve adherence, but experience with contraception shows that they can also be subject to coercion. This history should inform MPT development, training, and service delivery.
- Efforts to remove barriers to access can have unanticipated effects on other aspects of service delivery and use. For example, emergency contraception (EC), a user-controlled, coitally-related method is available without prescription in many settings. While this has made it easier for many women to obtain EC, it has also limited capacity to monitor product and service quality, and use.
- Defining "success" and expectations for uptake will be important to framing product introduction and diffusion. Varied metrics for "success" could include: access to all woman who want the product; reaching a certain public health impact; or sufficient volume to lower the price. Each may suggest different strategies for product introduction and roll out.

Integrating End-User and Provider Perspectives into MPT Development

To ensure that new health technologies can and will be used by people at risk, development efforts need to be informed by user and provider perspectives. Panelists reflected on lessons from microbicides currently under development, as well as barrier methods and the HPV vaccine already in use. Using the MPT Target Product Profiles (TPPs) described earlier as a starting point, they suggested product parameters that may be important for adherence, uptake and ongoing use.

- TPPs should be expanded to include product parameters highlighting end user and provider perspectives, ensuring that these considerations are central factors in defining TPPs.
- The concept of "users" encompasses a range of different actors who will influence product use: the person who will use the product ("end-user"); the person's family who will endorse/accept use; health professionals who will advise on use; and community members whose views will influence use. In many settings, product developers, policymakers and donors will also influence or even determine what products are developed and made available.
- Ideally, women should have options for products with different dosage formulations, delivery systems, and duration of use, such as pericoital gels, tablets, and films; sustained release rings, and user-independent injections and implants.

- For contraceptive (and other) methods, it will be important to provide accurate information to the end-user as to effects on fertility, including how quickly fertility returns, and any possible long-term effects.
- We will need to consider the reproductive health needs of women who wish to become pregnant, but who are at risk of HIV or STI. Therefore, MPTs providing protection from pregnancy, HIV, and/or STI must be available, as well as options that prevent HIV and/or STI but are non-contraceptive.
- While the technology differs from many MPTs being developed, experience with HPV vaccines offers some instructive lessons from users and providers. For users, the main areas of concern were: the route of administration, including pain and side effects from injection; safety concerns, especially effects on fertility; understanding who was in the target group for vaccination and why (given the focus on girls); and cost, in cases where cost sharing was expected. Providers were also concerned about cost, as well as several other areas relevant to their role: interacting with a new target group; the timing and number of doses needed for coverage; their own ability to explain the vaccine and its action; and sensitivity to heat and freezing.

Donor Perspectives and Potential for Public-Private Collaboration on MPTs

Building collaborations across sectors is also critical in the funding arena. Marshalling support from public, philanthropic, and private sector funding sources across disciplines will be critical to building a core of funding sufficient to support a robust pipeline. A number of private and public sector donors summarized their ongoing and upcoming work related to multipurpose prevention technologies. These efforts encompass a wide range of activities including basic research, product development, behavioral and other social science research, regulatory policy and advocacy.

- USAID is currently supporting MPTs through a five-year co-funding arrangement between the Offices of Population and Reproductive Health, and HIV/AIDS. In addition to support for the IMPT, this effort also funds the Population Council to clarify regulatory pathways for MPTs, as well as three different MPT R&D projects: the SILCS diaphragm with tenofovir gel (CONRAD); a tenofovir plus levonogstrel vaginal ring (CONRAD), and formulation of dapivirine plus a hormonal contraceptive in a vaginal ring (IPM).
- National Institutes of Health (NIH) representatives noted that the Institutes' leadership is increasingly focused on breaking down "silos" of research and other activity through integrating programs across branches and disciplines. This is especially relevant and encouraging for an area such as MPTs that, by definition, involves multiple approaches and disciplines. This broad and evolving approach at NIH encompasses a number of specific initiatives:
    - **NIAID** focuses on basic research, particularly innovation and new approaches to create and enable a sustainable product pipeline through two different divisions. The **Division of AIDS (DAIDS)** continues to support the discovery and clinical testing of HIV prevention strategies, through a series of research initiatives. The Integrated Clinical/Preclinical Program for HIV Topical Microbicides (IPCP-HTM)

has been the flagship program for these efforts in topical microbicides. The program is currently planning to include support for preclinical and early clinical testing of MPTs in future iterations of the IPCP program. The program is also planning to address potential needs for discovery and development of new MPT strategies. The Microbicides Innovation (MIP) and Next Generation PrEP (NGP) Programs are scheduled to be replaced with a new initiative that will include discovery and early development of MPT strategies in addition to supporting discovery of PrEP and microbicide candidates. The **Division of Microbiology and Infectious Diseases (DMID)** supports work on the traditional (non-HIV) STIs and associated RTIs and syndromes. A current RFA focuses on multipurpose prevention strategies that address at least two indications through single or combination products (at the time of the Symposium, awards were in process). The branch is particularly interested in work that moves new leads into clinical and translational research, thereby demonstrating the results of research and their implications for the public. It is important –and challenging – to balance multiple risks and multiple product needs. In the US one of the main perceived risks is HSV among the college age population. Messages emphasizing the overlapping risks of various STIs and RTIs, their relation to HIV risk, and the importance of preserving fertility, could highlight the importance of MPTs.

  - **National Institute of Child Health and Human Development (NICHD)** has been undergoing substantial changes. Reproduction and contraception remain core elements of its work, although the specific parameters related to MPTs are still evolving. Consistent with this more integrated approach, recently several branches within NICHD jointly issued an RFA on HIV acquisition and transmission that elicited a tremendous response.
  - The **Office of AIDS Research (OAR)** funds the Institutes to support innovative research, and also provides funds to bring experts from inside and outside NIH together to advance key issues. Its support often plays an important role in leveraging funding and highlighting new and emerging areas. OAR's annual plan of priorities and strategies mentions MPTs as an important area for study, and several of the priorities are directly related to MPTs, including microbicides, women and girls, and HIV prevention.

- In addition to its Dual Protection Initiative described above (see pp 4-5), the **Bill and Melinda Gates Foundation** is currently developing a strategy on contraception with potential for stronger connections with HIV and STI prevention in the future. There are several existing mechanisms with the BMGF such as the Grand Challenges that could be vehicles for supporting work on MPTs. The Foundation is considering areas in addition to product development, including advocacy, partnerships with the commercial sector, and implementation science.
- The **Mary Wohlford Foundation** highlighted the potential of **small private foundations** as sources of support for work on MPTs. Most small and medium private foundations do not have the resources to support large R&D efforts, but many may be open to the compelling case for MPTs in the US as well as internationally. Their more

modest contributions could fund discrete elements of research, or ancillary work in advocacy, information dissemination, and other critical activities.

Fostering Political Leadership for MPTs

Fostering champions and political leadership will be critical to maintain donor support and public interest through what may be lengthy and uncertain scientific processes. Panelists from diverse settings were asked to identify opportunities for building leadership and support for MPTs where they work and offered a number of observations and suggestions.

- Given the technical nature of MPT research and development, it is critical to "translate" research into information that can be presented to diverse audiences, especially policymakers and the media.
- Advocates and champions should be willing to embrace advocacy approaches that garner attention, and have specific, actionable requests to put forward once they have that attention.
- A cadre of trained spokespersons, including providers, researchers, and end-users, should be employed at strategic periods to raise awareness about MPTs and develop a base of political support.
- Political leaders are looking for solutions, especially interventions that are feasible and cost-effective. In many settings, unintended pregnancy, unmet need for contraception, STIs, maternal mortality and HIV are very visible problems that politicians are challenged to address. MPTs can be framed and put forward as solutions that could help politicians address these significant social and health challenges.
- In some political settings, politicians and leaders are also challenged to develop and champion policies and approaches that advance rights and address inequality. In these contexts, approaches such as MPTs can contribute to promoting women's rights, advancing sexual and reproductive rights, and helping women who are poor and disadvantaged, thereby supporting politicians in meeting their political obligations to benefit the poor.
- Policy environments in a number of countries are conducive to advancing MPTs and present real opportunities for diversifying the scientific and political leadership in the field. India has dynamic academic and pharmaceutical sectors with capacity to advance technical innovation and conduct clinical research. Local funding for health research is growing and the political and economic environment is conducive to technical innovation. China also has a supportive policy environment where many administrators have technical backgrounds and support technological innovation to address social challenges. HIV and contraception are national priorities in China and as such may be able to attract special funds set aside for this purpose.
- National and international leaders worldwide are challenged to address a range of pressing health and development problems: population growth, the HIV pandemic, maternal mortality and morbidity, supporting the rights of women and girls, among many others. Many of these challenges are reflected in international agreements like

the Millennium Development Goals and United Nations General Assembly Special Session on AIDS. MPTs offer the possibility of meeting some of these challenges and obligations, and champions for MPTs should promote them based on contributing to these multiple complex goals.

Recommendations and Next Steps

The symposium provided a critical opportunity for researchers, advocates, donors, and other key constituents to take stock of progress on MPTs and look ahead to consolidate these gains as research continues. During lively presentations and discussions, speakers and participants reviewed and raised important aspects of developing and implementing MPTs, and made recommendations for advancing the field quickly and efficiently. These recommendations spanned a wide range of issues, including scientific approaches, funding opportunities, the importance of incorporating user perspectives, and considerations around implementation as integral to product development.

- **Target Product Profiles (TPPs)**. Defining Target Product Profiles (TPPs) based on the most relevant MPT product attributes and parameters is essential, both to prioritize donor investments and to guide developer strategies. This process must be dynamic and regularly informed by emerging data, with the resulting TPPs specifically linked to regulatory pathways. MPT development should continue to pursue methods that use hormonal, non-hormonal and barrier contraceptive approaches to provide more options for women with different risk profiles and product preferences.
- **Pipeline**. A sufficient, sustainable pipeline of MPT scientific concepts and product approaches is needed to allow prioritization and cross-use of infrastructure products. The pipeline should also include a range of approaches to allow for more product choice, flexibility in adapting and prioritizing products in response to new data, and greater responsiveness to women's needs across their lifetimes. Potential regulatory pathways should be mapped for those MPT products that are furthest along in development.
- **MPT Vaccines**. MPT vaccine development can build on the history of successful multipurpose vaccines developed to prevent other diseases. However, meaningful investment in the fundamental science associated with MPT vaccine approaches will be required to move this area of research forward. Attention to the timing of risk and the realities of product delivery will be important in determining what combination approaches will be most appropriate.
- **Hormonal Contraception**. Efforts to develop MPTs must continue to be informed by evidence around the interface between hormonal contraception and HIV. The IMPT and its constituency of researchers, advocates, funders and policymakers should continue to champion efforts to build and act on evidence in this critical area. These include supporting the upcoming WHO consultation to develop expert consensus on the relationship between HC and HIV, and developing and funding a research agenda to further understand the interaction between HC and HIV.
- **Acceptability and Use**. Product acceptability, potential for adherence, and eventual implementation must play a central role in MPT product design and development. The

IMPT should pursue approaches analogous to the TPPs that will help identify and organize approaches that will enhance the probabilities of successful uptake of MPT products. Adherence and use are critical for implementation success.

- **Engaging Regulators**. The IMPT should identify opportunities to engage regulatory authorities from diverse countries to inform them about MPT concepts and approaches, and elicit their perspectives and feedback in order to shape regulatory strategies for emerging products.
- **"Multipurpose Visits"**. To provide critical services to meet current needs while new products are being developed, the IMPT and its allies can work to encourage "multipurpose visits" to provide women with ways to address the dual risks of unintended pregnancy and unwanted infection. Encouraging service delivery that addresses women's multiple needs can also set the stage for determining how best to deliver MPTs in different clinic settings.
- **Defining Users**. Successful development and implementation of MPT products will depend on a broad definition of 'users' to better understand the barriers and enabling factors that will affect product uptake and use within all relevant environments: policy, health systems, and users.
- **Metrics for "Success".** Given the often lengthy time frames required for a new health product or innovation to become established, it will be important to identify realistic metrics for "success." This should include: 1) developing new approaches to allow for more realistic demand forecasts and more accurate linking of supply and demand, 2) an investment framework for introduction, and 3) strategies for ensuring adequate funding for introduction and roll-out.
- **Funding**. Even in the current challenging economic climate, for the MPT pipeline to grow and advance, it will still be crucial for donor agencies to maintain current levels of funding commitments and increase those as budgets allow. The field should also explore new sources of funding and investment, including a range of foundations, to support specific, perhaps smaller, pieces of the MPT R&D and introduction continuum.
- **Advocacy**. The IMPT should work to expand the constituency for MPTs through increased efforts to engage scientists, providers, advocates, policy-makers, donors and those working in and funding related fields. The objectives would be to form a cadre of new advocates in new sectors, and to advance the scientific and product development agendas.
- **Support Structures**. Regional efforts to highlight and build strong constituencies for MPTs should be guided by community thought-leaders and explore establishing national MPT teams involving potential end-users, community opinion makers and service providers.
- **Partnering**. MPT developers and advocates will need to seek and create innovative partnerships around products that bridge the for-profit sector in the developed world and needs in low resource countries with poorer populations

Looking Ahead

The MPT 2011 Symposium was one in a series of meetings and activities explicitly designed to advance the MPT Initiative in a strategic fashion. A subsequent meeting, that took place in London in early 2012, helped engage and integrate a wider set of ideas and more global actors. In addition, panel presentations proposed for major international meetings should also attract new scientific expertise and approaches. As this work advances, the results of efforts to date, recent developments in reproductive health research, and the current economic climate signal three areas for priority emphasis:

- The MPT products currently in clinical testing are heavily dependent on a few combination products, which may or may not prove sufficiently safe and/or effective. Continued, timely funding for the advancement of these "first-generation" products will be essential to informing the potential of such strategies and to setting the stage for sound, strategic pipeline management and funding going forward.
- The IMPT's efforts to map the product pipeline have provided a valuable foundation. These efforts should continue and diversify as the basis for fostering a full, frank, and well-informed understanding of the preclinical pipeline, its potential, and what fresh concepts might appropriately be drawn in to enrich and bolster it. Energy and craft are needed—and soon—to identify, analyze, and attract potential additions and creative approaches.
- After a decade of turmoil, there is much more real dialogue and collective support for HIV prevention research, for truly integrated reproductive health services, and for strategic, collaborative review and funding. These heartening and timely developments merit continuation and expansion to meet current economic and political challenges. This means that donors must keep talking, sharing, and seeking synergistic intellectual and financial engagement.

Developing a robust, diverse and sustainable pipeline for MPTs will require sustained and new resources – ideas and people, as well as funding. Opportunities for scientific exchange, innovative thinking and recruiting a range of new talent will build on existing approaches in new ways and attract fresh ideas and solutions. The IMPT is committed to continuing to this work, with long-time and a growing cadre of new partners that will offer the best chance of making these urgently needed technologies become reality.

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Special recognition goes to the following individuals for their help in organizing the Symposium: Elizabeth Callihan, Camille Harris (ARHP), and Kathryn Stewart (CAMI).

Supporting agencies: Ansell Health Care Products; Association of Reproductive Health Professionals; Coalition Advancing Multipurpose Innovations (CAMI); CONRAD; Gilead Foundation; Mapp Biopharmaceutical; Mary Wohlford Foundation; National Institutes of Health, Office of AIDS Research; Nanjing University; PATH; Population Council; Public Health Institute; University of California San Francisco; University of Witwatersrand; United States Agency for International Development.

This report presents the collective view of an international group of experts and does not necessarily reflect the decisions or stated policies of any of the institutions whose staff participated in the discussions or any of the organizations which supported the Symposium.