



U.S. Food and Drug Administration
Protecting and Promoting Public Health

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Post-Trial Responsibilities



Food and Drug Administration



Richard Klein

Office of Health and Constituent Affairs

September 18, 2014

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Post-Trial Provisions

- Introduced concept that after the conclusion of the study patients should be assured of access to the best proven intervention arising from the study.
 - Justice issue.

Arguments around this have dealt with whether subjects derive benefit from the trial and are no worse off at the end than the *status quo* prior to the trial, or of not participating, versus the harm of being denied access to that which they have contributed to.

FDA Requirements

- There is no FDA requirement for post-trial provision of a product being investigated, even if it seems effective
- Where there is preliminary evidence of safety and effectiveness, FDA may permit post-trial use of an investigational product under an IND/IDE* during the time an investigational intervention is being reviewed for marketing approval, but is not required

* Investigational New Drug Application/Investigational Device Exemption

FDA Requirements Regarding Foreign Trials

- 21 CFR 312.120 Foreign clinical studies not conducted under an IND
 - Requires study be conducted in accordance with good clinical practice (GCP)
 - the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials done in a way that provides assurance that the data and reported results are credible and accurate and that
 - the rights, safety, and well-being of trial subjects are protected
 - independent ethics committee (IEC)
 - obtaining and documenting the freely given informed consent of the subject

Limited Jurisdiction

- FDA does not have jurisdiction over foreign trials, except as they relate to applications submitted for consideration in the U.S. or under an IND
- Sponsors and researchers must consult with foreign regulatory authorities to ensure they conform with the specific requirements in the study country

Post-trial access: Considerations for protocol drafters and IRBs

- Prospectively determine whether participants on control arm will be given drug/biologic at end of trial, cross-over, or other design
- Determine monitoring plan for adverse events and response (medical care, compensation) for AEs
- Determine financial responsibilities for providing investigational agent, and for ancillary care
- Inform IRB and FDA of significant changes about the drug or biologic as they emerge

Moral and Legal Obligations

- Research plan and Informed consent
 - Sponsors should prospectively consider whether a post trial access plan is appropriate
 - If access will be provided, should be in the consent document
 - Creates an obligation to adhere to commitments made to research subjects in the consent

FDA Perspective

- Scientific evaluation of the trial results (and perhaps other trials) is necessary to determine/establish benefit, or superiority of a new treatment over another
- Requires willingness of individual sponsors, because they control the provision of investigational interventions after a trial

Regulatory Requirements

- FDA does not have regulations or guidance documents that require post-trial access
- Decision left to sponsor/researcher to provide post trial access
 - Or not

Monitoring and Reporting Requirements

- After a trial is complete, if the product continues to be made available FDA requires that monitoring and reporting of adverse events continue.
- Death or life-threatening adverse events should be reported to FDA within 7 days of receipt of information by sponsor

Post-trial Access is Not Appropriate in All Studies

- Significant safety concerns (e.g., where REMS* might be imposed once product is approved)
- Studies of biomarkers and potential endpoint surrogates – validation studies (not looking at safety and effectiveness)
- Exceptions exist: in some situations, agent may appear to be beneficial where no/limited other options exist

* Risk Evaluation and Mitigation Strategy

Post-trial Access is Not Always Feasible

- If additional drug/biologic does not exist (e.g. Ebola Rx)
- Insufficient supply to continue study AND provide outside trial
- Insufficient safety data or safety signal that appears to increase with exposure
- No practical capacity or resources to provide essential safety monitoring
- Financial limitations of sponsor (early biotech)

Expanded Access

Sponsors may wish to make promising medical products available outside of the clinical trial for treatment use, or once the trial has ended:

Access can be made available to

- Individuals
- Groups of individuals
- Large groups of patients

Requirements for all EAPs 21 CFR 312.305

- Serious or immediately life threatening illness or condition
- No comparable or satisfactory alternative therapy
- Potential benefit justifies the potential risks of the treatment, and those risks are not unreasonable in the context of the disease or condition being treated
- Providing drug for the expanded access use will not interfere with or compromise development

Human Subject Protections Apply to All EAPs

Drugs in EAPs are *investigational drugs*, and they are subject to the following requirements from 21 CFR:

- Part 50- Protection of Human Subjects (informed consent)
- Part 56- Institutional Review Board
- Part 312 - including Clinical Holds based on safety and reporting requirements (adverse event reports, annual reports)





[http://www.fda.gov/downloads/Drugs/
GuidanceComplianceRegulatoryInformation/Guidances/
UCM351261.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351261.pdf)

Guidance for Industry

Expanded Access to Investigational Drugs for Treatment Use — Qs & As

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments on the draft guidance to <http://www.regulations.gov>. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Colleen Locicero at 301-796-2270, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 301-827-1800.



[http://www.fda.gov/downloads/Drugs/
GuidanceComplianceRegulatoryInformation/Guidances/
UCM351264.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351264.pdf)

Guidance for Industry

Charging for Investigational Drugs Under an IND — Qs & As

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EAPs and Patients - Benefits

- Can provide access to patients with serious/life-threatening diseases who have no other alternatives, *and* may be willing to accept greater risk
- Can provide patients a measure of autonomy over their own health care decision
- The treatment IND can help bridge the gap between the latter stages of product development and approval by making a drug widely available during that period
- Can be a foothold into marketplace for sponsors
- May offer hope for patients with no other available options



How are Safety and Risk weighed for EAPs?

Evidentiary basis linked to size of exposed population and seriousness of disease

- Sufficient evidence of safety and effectiveness to support the use of the drug
- Reasonable basis to conclude the therapy may be effective and would not expose patients to unreasonable and significant risk – relative to the risk of the disease
- More rigorous requirements with increasing exposure -- makes access risk-benefit analysis analogous to the clinical trial phase 1, 2 and 3 paradigm of growing exposure



Need for Balance

- Treatment access must be balanced against the systematic collection of clinical data to characterize safety and effectiveness
- Patient autonomy must be balanced against exposure to unreasonable risks and the potential for health fraud, potential exploitation of desperate patients
- Individual needs must be balanced against societal needs
 - Clinical trials are the best mechanism to provide evidence of safety and effectiveness for potential new treatments
 - FDA approval for marketing is the most efficient means to make safe and effective treatments available to the greatest number of patients.

Could EAPs Impair Trial Enrollment?

- Early access to investigational therapies could make phase II and III clinical trials more difficult to perform
 - E.g., AZT for HIV, High Dose Chemotherapy + bone marrow transplant for stage IV breast cancer
- General agreement that access to experimental drugs can only be granted if clinical trial enrollment is unimpaired, but how is this practically done?
- Manufacturing capacity is often limitation in early phases – supply of drug for expanded access could limit supply for trials

Dispelling Myths

- **Application process is burdensome and time consuming**
 - Usually less than an hour or two for preparation
- **Process is too complicated**
 - FDA staff available to help physicians and counsel patients
 - FDA creating a simplified form specific to single patient requests
- **FDA takes weeks to months to process an application**
 - Normally 2-4 day turnaround
 - Emergency requests turned around in hours
- **Negative impact of adverse event data**
 - Adverse events not unexpected in these patients, often related to underlying disease
 - FDA reviewers experienced in discerning adverse events relationships
 - Four decades of experience without examples
- **FDA is the barrier to expanded access**



Expanded Access Submission Receipts	Reporting Period				Average
	10/13/2009-10/12/2010	10/13/2010-10/12/2011	10/1/2011-9/30/2012***	10/1/2012-9/30/2013***	
Expanded Access INDs					
Single Patient Emergency INDs received	516	443	289	315	391
Single Patient Emergency INDs allowed to proceed	500	442	287	313	386
Single Patient INDs received	484	652	498	550	546
Single Patient INDs allowed to proceed	484	652	496	550	546
Intermediate Size INDs received	2	0	14	28	11
Intermediate Size INDs allowed to proceed	2	0	14	27	11
Treatment INDs received	0	1	0	0	0
Treatment INDs allowed to proceed	0	1	0	0	0
Expanded Access Protocols					
Single Patient Emergency Protocols received	0	3	0	2	1
Single Patient Emergency Protocols allowed to proceed	0	3	0	2	1
Single Patient Protocols received	16	89	121	62	72
Single Patient Protocols allowed to proceed	16	89	121	62	72
Intermediate Size Protocols received	5	1	8	8	6
Intermediate Size Protocols allowed to proceed	5	1	8	8	6
Treatment Protocols received	7	11	10	12	10
Treatment Protocols allowed to proceed	7	11	10	12	10
Totals for Expanded Access					
Total Number of Expanded Access INDs and Protocols received in CDER	1030	1200	940	977	1037
Total Number of Expanded Access INDs and Protocols allowed to proceed	1014	1199	936	974	1031

***The third and fourth reporting period is different than the first two reporting periods. The reporting period for the first 2 periods started the day the final rule went into affect. The reporting period was changed to a fiscal year to match the reporting period for other IND submission receipts.



For Further Information

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Pharmaceutical Companies v. the State: who is responsible for post-trial provision of drugs in Brazil?

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NATIONAL HEALTH COUNCIL *RESOLUTION 251/1997*

IV. 1 - access to the medicine being tested must be assured by the sponsor or, if there is no sponsor, by the institution, researcher, or promoter in the event that its superiority over the conventional treatment is proven.

NATIONAL HEALTH COUNCIL *RESOLUTION 466/2012*

III.3 - Biomedical research studies of experimental methods involving human subjects, (...) should (...):

d) Ensure all participants at the conclusion of the study free access by the sponsor, and for an indetermined period, to the best prophylactic, diagnostic and therapeutic methods the efficacy of which have been demonstrated.

d.1) Access will also be ensured during the interval between the end of an individual participation and the conclusion of the study, which may occur through expanded access programs, according to the medical assessment of the physician assisting the participant.

NATIONAL HEALTH SURVEILLANCE AGENCY

RESOLUTION 32/2013

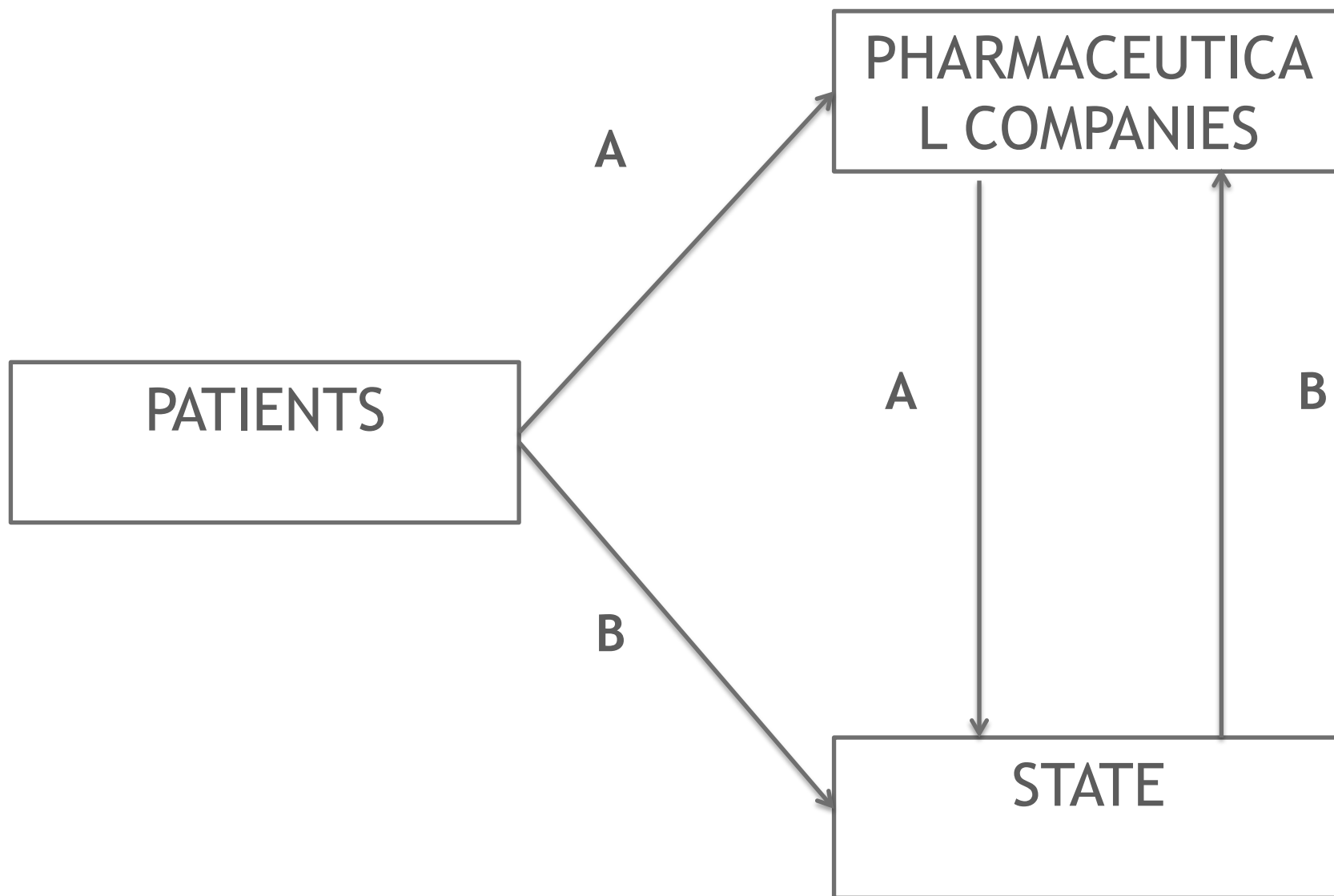
- Regulates compassionate use, expanded access and post-trial access programs
 - Art. 15 - Access to drugs after a trial is concluded will be provided to the subjects of the research for free, so long as it is beneficial, according to medical criteria;
 - Art. 16 - Sponsors are responsible for (...) providing PTA free of cost; monitoring the patients; providing care in case of side effects.

FEDERAL CONSTITUTION

- Art. 196. Health is a right of all and a duty of the State.

PTA in courts

- Schering (State of Rio Grande do Sul)
- Genzyme (State of Rio Grande do Sul)
- Biomarin, Genzyme and Shire (State of Sao Paulo)



Harvard MRCT Post-Trial Responsibilities Conference: Ethics and Implementation



Jocelyn Ulrich, MPH

Director, Scientific and Regulatory Affairs

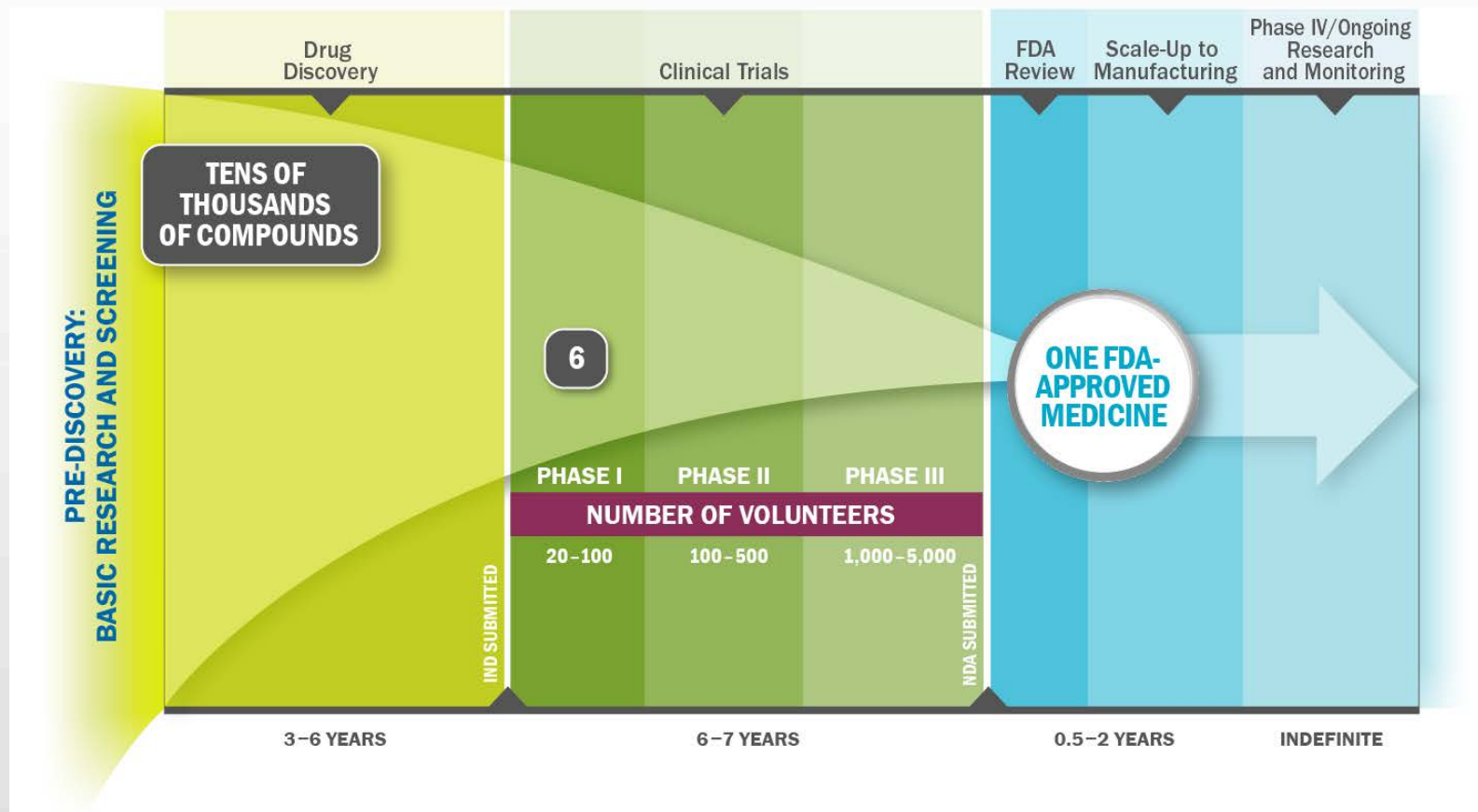
PhRMA
RESEARCH • PROGRESS • HOPE

Outline

- Clinical Research Across the Globe
- Industry Commitment
- Post-Trial Access to Medical Care - Background
- What is the Sponsor's Role and Responsibilities in Post-Trial Access?
- Discontinuing Access to Study Medication
- Approved Medications
- Conclusion

The Research and Development Process

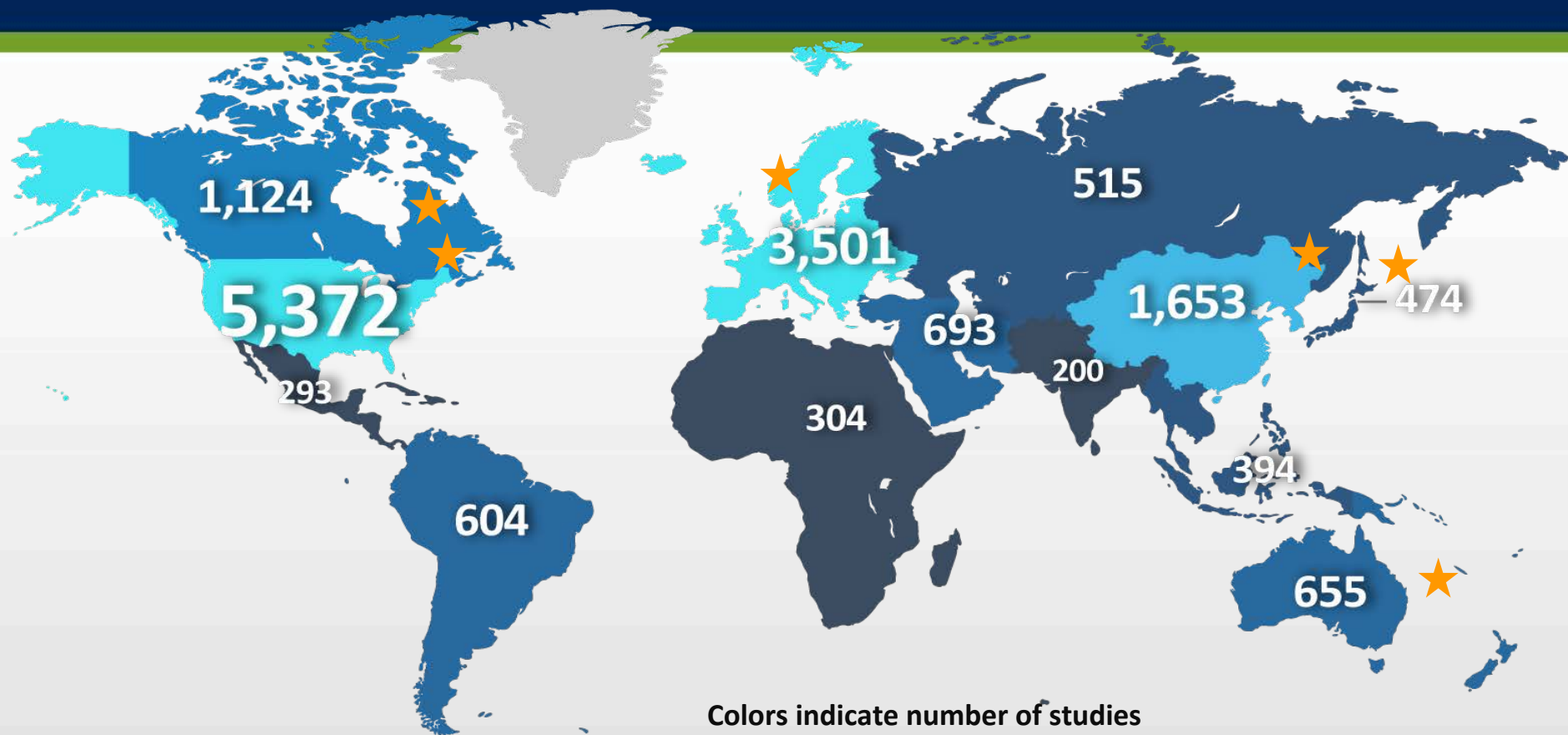
Developing a new medicine takes an average of 10 to 15 years.*



*This is not inclusive of all approval pathways, such as expedited or breakthrough.

Source: PhRMA¹

Clinical Research Across the Globe



Colors indicate number of studies
with location in that region

Least  Most

Labels give exact trial count*

*Based on open, interventional studies by Industry available on June 13, 2014.

Biopharmaceutical Industry Commitment

- **Biopharmaceutical companies are committed to high-quality clinical research that is:**
 - Scientifically and ethically rigorous
 - Fully compliant with all legal and regulatory requirements
- **PhRMA highly values the fundamental principles of the Declaration of Helsinki and acknowledged this document in its own voluntary principles**
 - Principles on Conduct of Clinical Trials and Communication of Clinical Trials Results (*PhRMA, 2009*)

“In sponsoring and conducting clinical research, PhRMA members place great importance on respecting and protecting the safety of research participants. Principles for the conduct of clinical research are set forth in internationally recognized documents, such as the Declaration of Helsinki and the Guideline for Good Clinical Practice of the International Conference on Harmonization.” 36

Post-trial Access to Medical Care: Background

- **PhRMA recognizes the value of clearly defining what constitutes post-trial access**
- **Limited clarity is provided in the Declaration of Helsinki or other ethical guidance documents about:**
 - What constitutes post-trial medical care
 - Which populations/s should receive post-trial access to medical care
 - Who is responsible for providing post-trial access to medical care
 - When post-trial access to medical care could/should end
- **Our comments relate to post-trial access to trial medications**

What is the Sponsor's Role and Responsibilities in Post-trial Access?

- The sponsor may choose to offer post-trial access to trial medications in specific circumstances (*e.g., life-threatening diseases, clinical emergencies*) for which no appropriate alternative therapies are locally available:
 - Subject to local legal and regulatory requirements
 - Guided by the best available evidence for a favorable benefit/risk profile
- Plans for post-trial access (including discontinuation) should be guided by a documented pre-trial agreement and any potential modifications

Discontinuing Post-trial Access to Study Medication

- **In cases where the sponsor plans to provide post-trial access to the study medication, supply may be discontinued if:**
 - In the sponsor's opinion, new information becomes available that negatively affects the previous benefit/risk assessment of the medication
 - The reviewing agency rejects the request for marketing authorization based upon an assessment of benefit/risk and there are no further plans to seek authorization
- **In all circumstances, the sponsor should work with relevant local healthcare authorities and services in the best interest of the trial participants**

Post-trial Access to Medical Care

– Approved Medications

- **Post-trial access to medicines that have achieved market authorization should be the responsibility of the applicable government agency or other payers through their healthcare systems**
 - The sponsor should not be responsible for any continued healthcare costs for diseases/conditions

Conclusions

- Biopharmaceutical companies conduct clinical research globally, and PhRMA members place great importance on respecting and protecting the safety of research participants
- Plans for post-trial access (including discontinuation) should be guided by a documented pre-trial agreement on a case-by-case basis, created in consultation with all relevant stakeholders
- Access to approved medications should be the responsibility of the government agency or other applicable payers through their healthcare systems

Post-Trial Responsibilities Conference:

Ethics and Implementation

Ramadhani A. Noor

September 18, 2014:

Key Questions

- **What is the role of investigators when it comes to PTA**
- **What is typical & what can investigators realistically do**
- **What are the implications of imposing responsibilities on investigators**



Licensed products that sits on a shelf are useless



Guidelines – CIOMS 2002

Guideline 10: “before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:

- research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
- any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.”

...that a disease is
needed: the ethical
interventions or other
is applicable
lack the resources to

Guidelines – CIOMS 2002

Guideline 10: *“before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:*
- *research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and*
- *any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.”*

Guideline 10 Commentary: *“It is not sufficient simply to determine that a disease is prevalent in the population and that new or further research is needed: the ethical requirement of ‘responsiveness’ can be fulfilled only if successful interventions or other kinds of health benefit are made available to the population. This is applicable especially to research conducted in countries where governments lack the resources to make such products or benefits widely available.”*

Guidelines – Declaration of Helsinki

Paragraph 30 of the 2000 version: *“At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.”*

Paragraph 30's accompanying note of clarification, version of 2004: *“The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.”*

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Other Guidelines – Over time

- The US Code of Federal Regulations does not mention PTA ([45CFR46, revised 2009](#)).
- Some major sponsors of research are prohibited from funding PTA ([NIH Group, 2005](#))
- Facilitates investigators to take over the responsibility ([Wellcome Trust Group, 2013](#)).

The reality in developing countries..

- **Often efficacious standard of care doesn't exist** [Edward C, Jones-López et al, 2011]
- **Inadequate mechanisms for expanded access to research products**
[Emergency use, Compassionate use, Treatment use & Continued use]
- **Limited financing mechanisms for PTA**
- **Weak Decision Making Frameworks**

Traditional delays in introducing approved products especially in developing countries

Jerome Singh; The Challenge of Discharging Research Ethics Duties in Resource-Constrained Settings PLOS| MEDICINE: March 15, 2011

Effectiveness of the Standard WHO Recommended Retreatment Regimen (Category II) for Tuberculosis in Kampala, Uganda: A Prospective Cohort Study: Edward C, Jones-López et al, PLOS| MEDICINE March 2011



**Support
Legal Action
against
GlaxoSmithKline
& Boehringer Ingelheim!**

Many people with HIV/AIDS need:
• AZT • Lamivudine • Nevirapine
everyday to live!



THE LANCET Infectious Diseases

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The Lancet Infectious Diseases, Volume 2, Issue 8, Page 452, August 2002
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Court ruling orders South Africa to provide nevirapine

Tom Das

After nearly a year of intense courtroom battles, South Africa's constitutional court has quashed the government's appeal to overturn the high court order that nevirapine must be provided in [hospitals](#) state-wide. "[The] government is ordered without



Lessons From Global Vaccine Development Programs [Malaria]

Global

Regulatory: EMA positive scientific opinion

Policy: WHO policy recommendation and pre-qualification

Financing: GAVI, other donors

National

Financing: GAVI co-pay, other

Policy: Government decides to adopt and requests vaccine

Regulatory: NRA approval



A set of complex processes that run in parallel and are also linked, must be completed for introduction of RTS,S to begin.



The rest of Development Countries not exceptional...

“Given the magnitude of malaria and lack of a vaccine, every person in the country is at risk and given the traditional delays between the introduction of a new medical solution and their implementation, our country must begin to prepare for malaria vaccine introduction now.”

***Dr Pascoal Mocumbi, former Prime Minister of
Mozambique***

Influencing policy: Many questions need answers on introducing new products

- ? Disease burden
- ? Economic burden
- ? Other existing interventions
- ? Among available intervention, which one gives greatest public health impact
- ? Which interventions are cost effective
- ? Which combination of interventions to adopt
- ? Can a country afford the product if it proves to be cost effective
- ? If not who will pay for the product
- ? What financing options does a country have
- ? Can the current health infrastructure accommodate delivery of the product
- ? What other factors should be considered

Depending on national circumstances each country will answer differently

Need for early country level planning

Example: Malaria Vaccine Decision-Making Framework

REGIONAL MALARIA VACCINE DECISION-MAKING FRAMEWORK — DATA (SIMPLIFIED)

Key: National level data Global level data

	PRE-LICENSURE (5 YEARS)	AVAILABLE DATA - PHASE III	LICENSURE (2 YEARS)	POST-LICENSURE (5 YEARS)
				MALARIA VACCINE INTRODUCTION DECISION
MALARIA DISEASE BURDEN	<ul style="list-style-type: none"> Confirmed malaria cases by age group Malaria cases in pregnant women and HIV+ individuals Epidemiological profile 		<ul style="list-style-type: none"> Update on current malaria situation 	<ul style="list-style-type: none"> Confirmed malaria cases by age group
OTHER MALARIA INTERVENTIONS	<ul style="list-style-type: none"> Impact of current malaria interventions Coverage and Country-specific impact of current malaria interventions 			<ul style="list-style-type: none"> Changes in impact and cost effectiveness of other anti-malaria interventions
MALARIA VACCINE IMPACT	<ul style="list-style-type: none"> Projected impact on mortality and morbidity in different age groups 	<ul style="list-style-type: none"> Marginal impact with other malaria interventions 		<ul style="list-style-type: none"> Vaccine coverage
ECONOMIC & FINANCIAL ISSUES	<ul style="list-style-type: none"> Preliminary cost-effectiveness estimates of malaria vaccine 	<ul style="list-style-type: none"> Vaccine price for public Donor subsidy for vaccine National affordability 	<ul style="list-style-type: none"> Sustainable national commitment 	<ul style="list-style-type: none"> Updated malaria vaccine cost data Estimates of recurrent costs
EFFICACY, QUALITY, & SAFETY	<ul style="list-style-type: none"> Safety Adverse events Interaction with other vaccines Efficacy 	<ul style="list-style-type: none"> Impact on clinical and severe disease, anemia, etc. Duration of efficacy of the vaccine 	<ul style="list-style-type: none"> Efficacy, Quality, and safety data from other countries 	<ul style="list-style-type: none"> Post-licensure safety and efficacy data
PROGRAMMATIC CONSIDERATIONS	<ul style="list-style-type: none"> Anticipated vaccine characteristics and presentation Evidence of institutional pathways to support intervention 	<ul style="list-style-type: none"> Demand forecast HS capacity for malaria vaccine Supply availability Product information for storage 	<ul style="list-style-type: none"> Targeted groups Communications plan Evidence of institutional support for interventions 	<ul style="list-style-type: none"> Evidence of supply security

The DMF outlines information and processes required for timely and informed decisions when an approved malaria vaccine becomes available – [A tool to aid systematic planning]

Summary

- Legal frameworks and Mechanisms for expanded drug access need to be developed for developing countries regulatory authorities
- Evidence to support decision making/ plans for PTA should be generated in parallel with product development [DMF / Implementation Science]
- Partnerships [PPPs – Investigators, sponsors, funders/ philanthropy, governments, global development agencies etc]

A close-up, profile view of a young child's face, looking upwards and to the left. The child has dark skin and large, dark eyes. The lighting is warm and soft, highlighting the contours of the face. The background is a solid, vibrant green.

THANK YOU

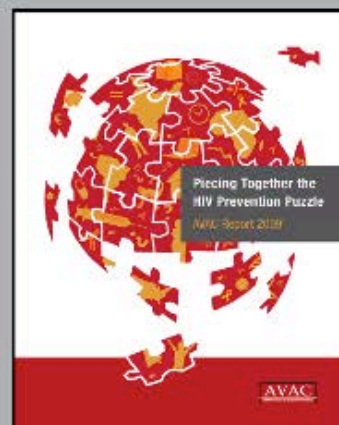
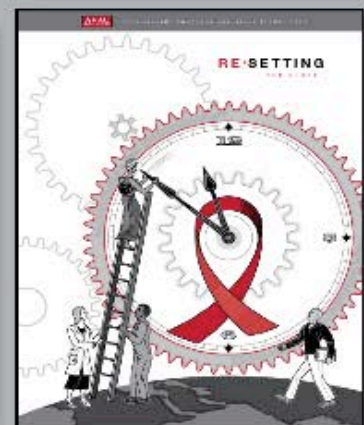
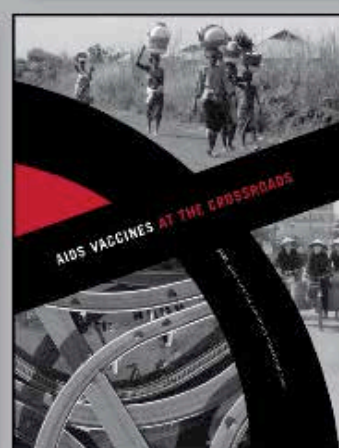
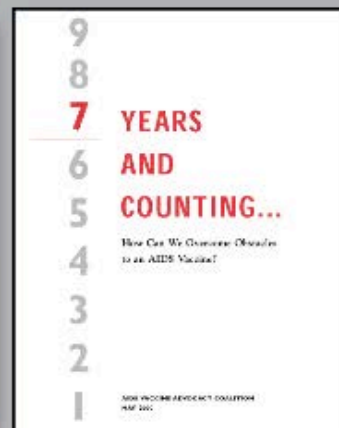
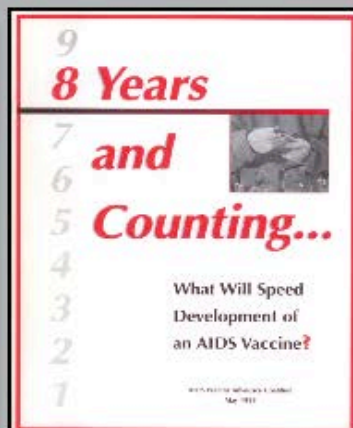
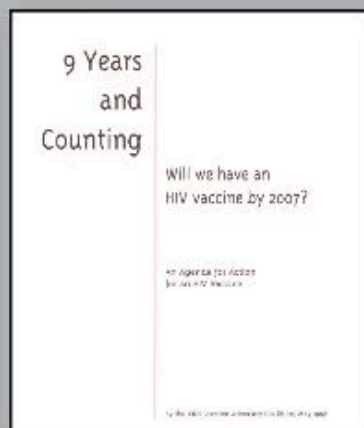
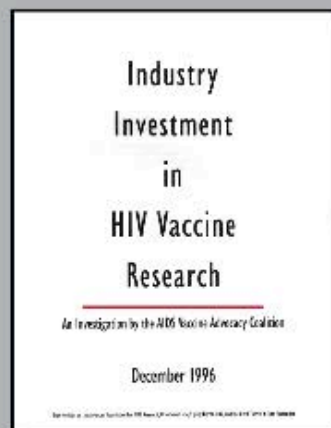
Post-Trial Access

An Advocate's Perspective

Mitchell Warren
Executive Director, AVAC
September 18, 2014

About AVAC

- Founded in 1995 as the AIDS Vaccine Advocacy Coalition
 - Promote increased funding and investment in HIV vaccine research by government agencies, private industry, and non-governmental organizations;
 - Identify barriers to the development of a vaccine; and
 - Increase public awareness of the need for a well-funded, coordinated HIV vaccine research program.
- Since 2004: use education, policy analysis, advocacy and a network of global collaborations to ***accelerate the ethical development and global delivery*** of new HIV prevention options as part of a comprehensive response to the pandemic



The End?

AVAC
United Advocates for HIV Prevention
REPORT 2011

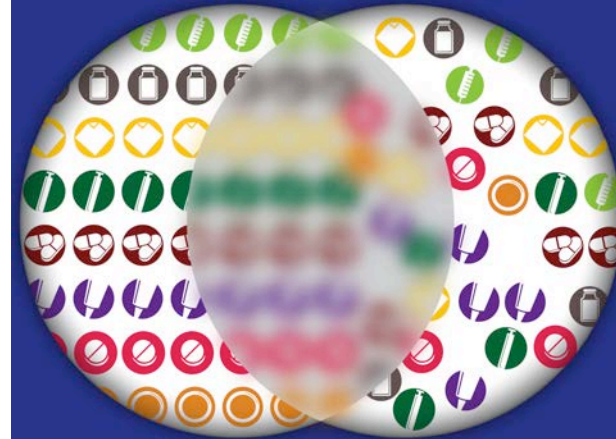
ACHIEVING THE END

ONE YEAR
AND
COUNTING

The End?

AVAC
United Advocates for HIV Prevention
REPORT 2012

AVAC REPORT 2013: Research & Reality



AVAC
United Advocates for HIV Prevention
www.avac.org



A Three-Part Agenda for Ending AIDS

Deliver proven tools for immediate impact

- Align programs, models and funding to stay on track to end AIDS.
- Expanded testing and viral load monitoring
- Treatment
- Voluntary medical male circumcision
- Female and male condoms
- Prevention of pediatric infection
- Syringe exchange programs

Demonstrate and roll out new HIV prevention tools

- Plan for immediate follow-up on current gel and ring trials, regardless of results.
- Map the pathway beyond pilot projects.
- Daily oral TDF/FTC as PrEP
- Non-surgical devices for voluntary medical male circumcision
- 1% tenofovir gel

Develop long-term solutions to end the epidemic

- Safeguard HIV prevention research funding.
- Launch complex trials to answer complex questions.
- Don't abandon user-dependent methods.
- AIDS vaccines
- Cure
- Multipurpose prevention technologies
- Next-generation ARV-based prevention
- Non-ARV-based microbicides
- Rectal microbicides

GOAL: A sustained decline in HIV infections (currently at 2.3 million/year)

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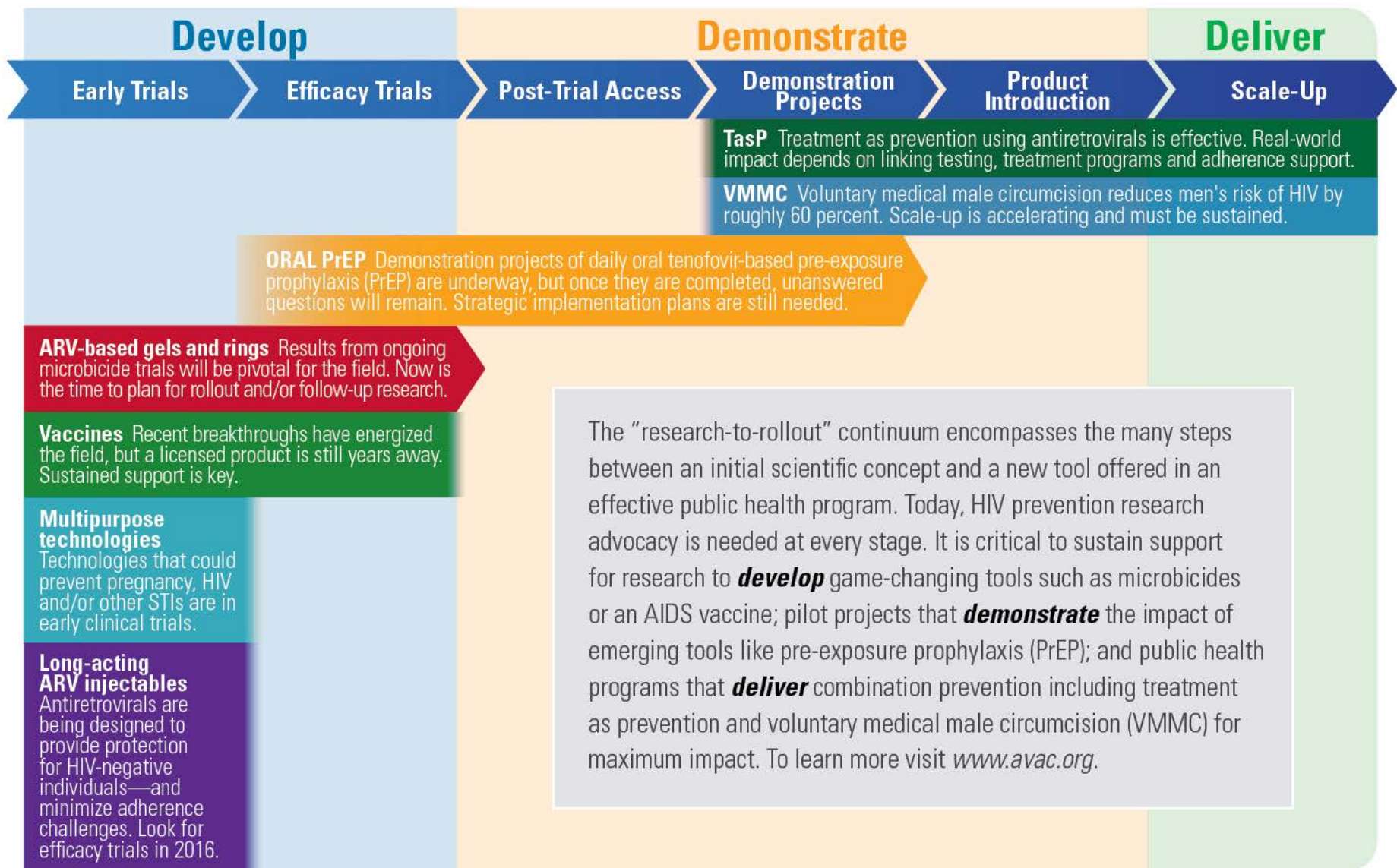
Years to impact

Zero to 5

5 to 10

10 to **End**

→ The HIV Prevention Research-to-Rollout Continuum, December 2013



PrEP 2004



2007 (updated 2011)

Good participatory practice guidelines for biomedical HIV prevention trials



Good participatory practice guidelines for biomedical HIV prevention trials 2011

Why GPP

- In response to PrEP trial controversies in 2004/2005
- Help prevent misunderstanding and miscommunication among research stakeholders
- Premise: what happens with one product, one trial, one region can affect all – trial participants, research teams, funders, sponsors, community stakeholders, and product developers
- Just as other aspects of clinical trials are informed by guidelines, so too the relationship between research entities and stakeholders
- GPP guidelines were developed to facilitate building of effective, durable partnerships among all stakeholders

Did You Say GCP?

GCP ≠ GPP

**Research
Investigator**

GCP



**Trial
participants**

**Research
teams
(and trial
sponsors and
funders)**

GPP



Stakeholders

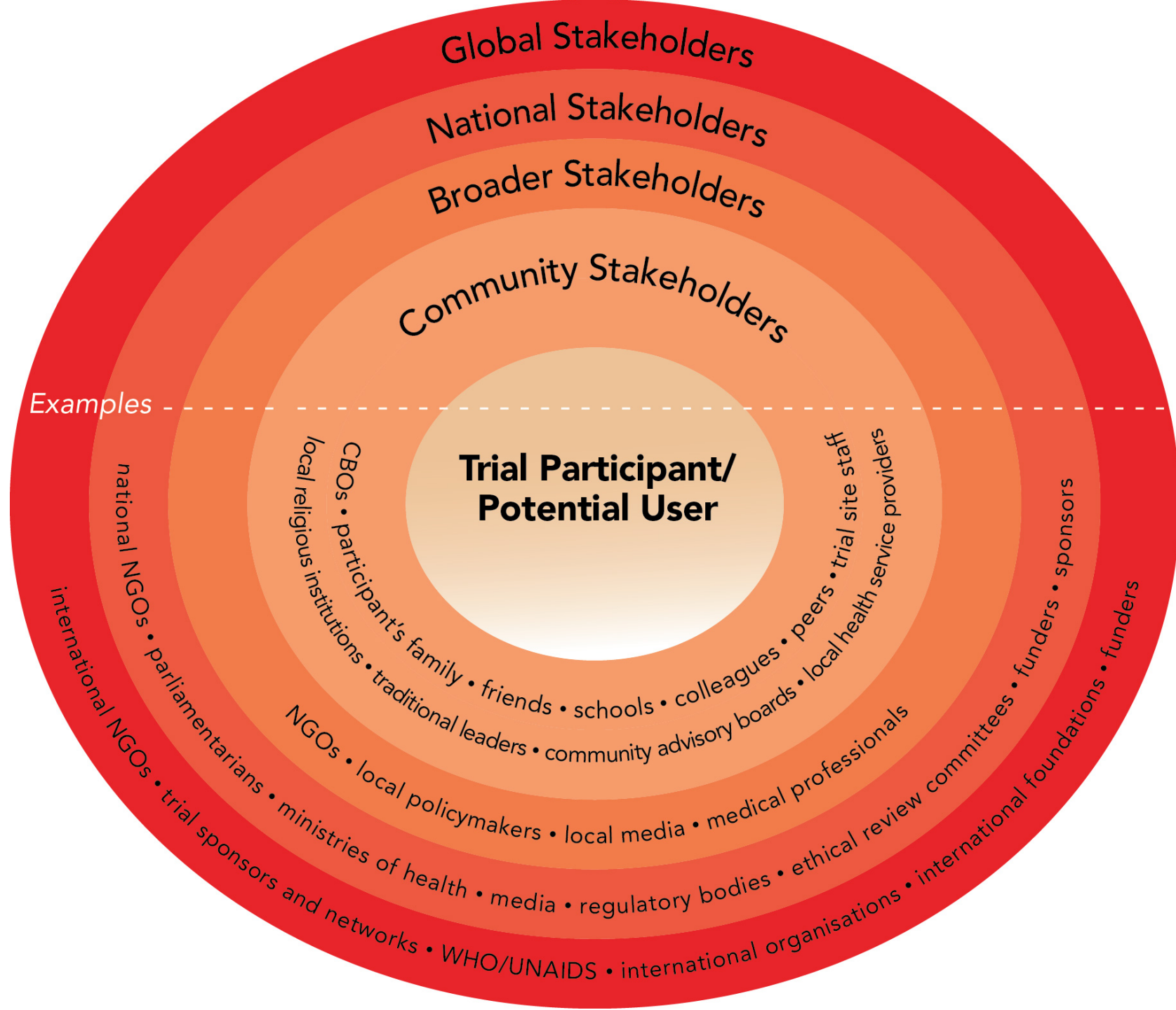
Stakeholders

Stakeholders

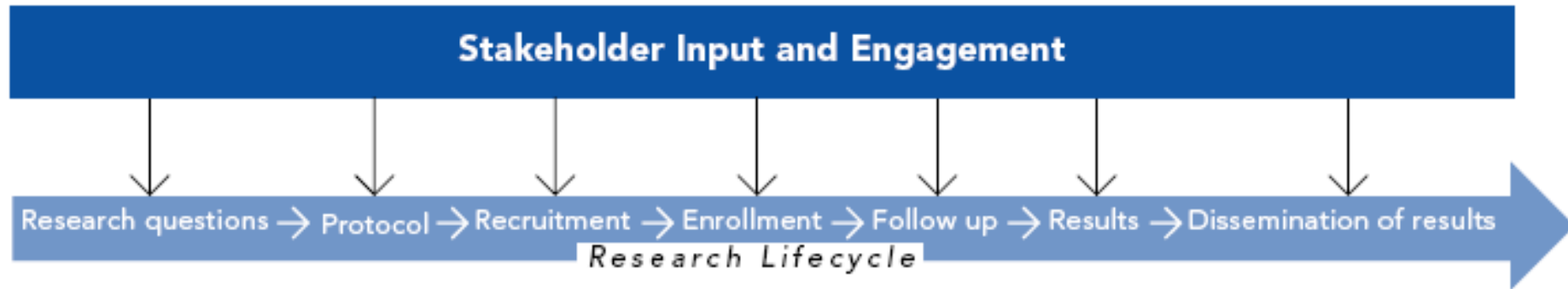
Stakeholders

Stakeholders

Stakeholders



It's a Journey



- Process through which trial funders, sponsors, and implementers build meaning relationships with stakeholders
- Goal is to shape the research process by using the expertise of stakeholders
- It is *not* recruitment!

GPP Guidelines, 2nd Edition

Section 1:

The Importance of Good Participatory Practice

The Importance of Good Participatory Practice

defines the key terms used in the document and describes the realities and the underlying determinants of the HIV epidemic, the context of conducting biomedical HIV prevention trials, and why a participatory approach is necessary to effectively conduct trials.

Section 2:

Guiding Principles of GPP in Biomedical HIV Prevention Trials

Guiding Principles of GPP in Biomedical HIV Prevention Trials

outlines the set of principles that serve as the foundation of the relationships among trial funders, sponsors, and implementers and other stakeholders.

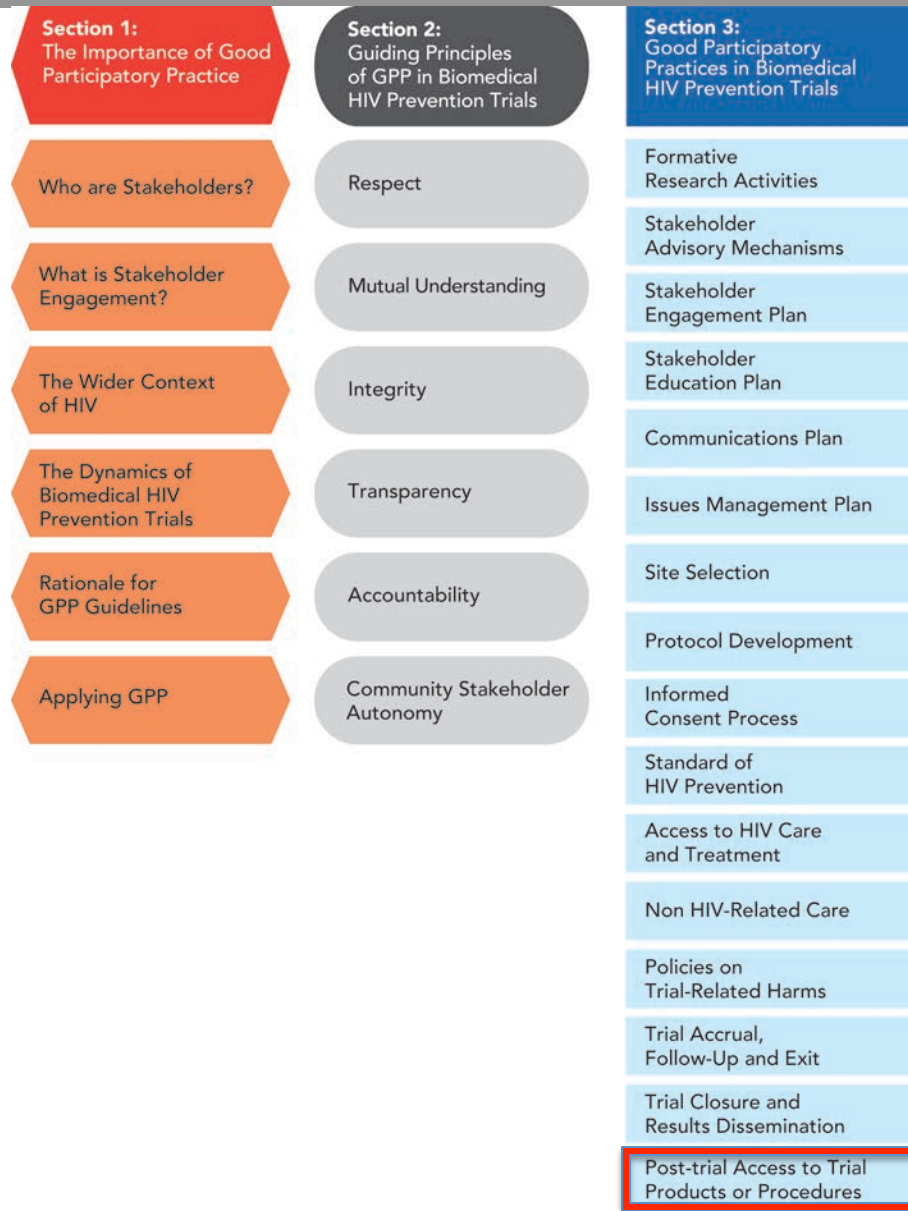
Section 3:

Good Participatory Practices in Biomedical HIV Prevention Trials

Good Participatory Practices in Biomedical HIV Prevention Trials

describes optimal practices for trial funders, sponsors, and implementers to follow when designing, conducting, and concluding biomedical HIV prevention trials. Under 16 topic areas, this section outlines expected stakeholder engagement activities that take place at each stage of the research life-cycle.

Sections of the GPP Guidelines



GPP on Post-Trial Access

3.16 Post-trial access to trial products or procedures

3.16.A. Definition

The term “post-trial access to trial products or procedures” refers to making the prevention product or procedure tested in the trial available to trial participants and local community stakeholders (1) should the new product or procedure be scientifically validated or approved by relevant authorities, and (2) in the form of follow-on, open label, or other such studies before product licensure or approval, should an efficacy or effectiveness trial have a compelling positive finding, with no safety concerns.

3.16.B. Relevance to good participatory practice

Research ethics call for maximising benefits to stakeholders who participate in research. Thus, local community stakeholders are to be among the first to gain access to new prevention products should they be found safe and effective. How trial sites communicate and interact with community stakeholders about issues of access to the prevention product or procedure studied is likely to have a significant influence on community stakeholder perceptions of a trial.

3.16.C. Special considerations

1. Availability of newly identified products or procedures to trial participants and other community stakeholders will depend on the biomedical HIV prevention strategy being tested.
2. After a trial is completed, other trials may be needed to corroborate findings.
3. After results from relevant trials are available, it may take time for normative agencies and appropriate regulatory authorities, including national governments, to approve the new product or procedure. Approval processes and timelines will differ by product or procedure and by country.
4. National regulatory authorities make the ultimate decision about whether a new product or procedure will be approved for use within a particular country.
5. Availability and pricing of new products or procedures may be affected by product-manufacturer parameters as well as by agreements with trial sponsors.

3.16.D. Good participatory practice practices for post-trial access to trial products or procedures

1. Research teams discuss with relevant stakeholders, early in the trial process, issues affecting future product or procedure availability, including the need for corroborated biomedical evidence, pursuit of licensure, production rights, and additional marketing and distribution research.

2. Trial funders, sponsors, and research teams conducting efficacy or effectiveness trials discuss with relevant stakeholders, early in the trial life-cycle, expectations about possible pre-licensure access, plans for follow-on, open label, or other such studies, and how such pre-licensure access will be funded, in the event that a compelling positive result, with no safety concerns, is observed.
3. Trial sponsors and research teams discuss, negotiate, and agree on responsibilities and funding requirements with national governments concerning licensure requirements and access issues, should the HIV prevention product or option under investigation be shown to be safe and effective.
4. Trial sponsors and research teams develop a clear strategy and funding mechanisms for how the HIV prevention product or procedure will be made available to participants (at a minimum) rapidly, affordably, and sustainably, should the HIV prevention product or procedure be shown to be safe and effective. Sponsors and research teams can collaborate with multiple stakeholders, such as UN organisations, development partners, local governments, and non-governmental organisations to design and support the overall access strategy.
5. Research teams inform community stakeholders of their rights, the access plan, and the factors that could postpone or prevent their gaining access to the new prevention product or procedure, such as the need to secure regulatory approvals or parameters related to the product manufacturer. Research teams give community stakeholders updates as they are available.

3.16.E. Additional guidance

1. *Ethical considerations in biomedical HIV prevention trials* (Guidance Point 19, page 60, Availability of Outcomes).¹
2. *Rethinking the Ethical Roadmap for Clinical Testing of Microbicides: Report on an International Consultation* (Chapter 10, After the trial: continued access and post-approval studies).³⁷
3. *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (Recommendation 4.1).³⁸

GPP on Post-Trial Access

- Research teams discuss with relevant stakeholders, early in the trial process, issues affecting future product or procedure availability
- Trial funders, sponsors & research teams discuss with stakeholders, early in the trial life-cycle, expectations about possible pre-licensure access, plans for follow-on, open label, or other studies, and how pre-licensure access will be funded
- Trial sponsors and research teams discuss, negotiate, and agree on responsibilities and funding requirements with national governments concerning licensure requirements and access issues, should product or option be safe and effective

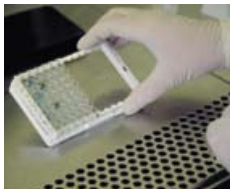
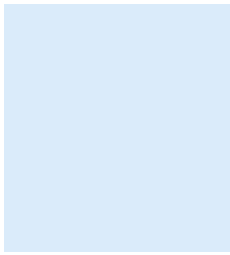
GPP on Post-Trial Access

- Trial sponsors and research teams develop clear strategy and funding mechanisms for access to participants (at a minimum) rapidly, affordably, and sustainably, should the HIV prevention product or procedure be shown to be safe and effective. Sponsors and research teams can collaborate with multiple stakeholders, such as UN organisations, development partners, local governments, and NGOs
- Research teams inform community stakeholders of their rights, access plan, and factors that could postpone or prevent their gaining access to product or procedure, such as regulatory approvals or parameters related to product manufacturer. Research teams give stakeholders updates as available.

UNAIDS Ethics on Post-Trial Access

Ethical considerations in biomedical HIV prevention trials

UNAIDS/WHO guidance document



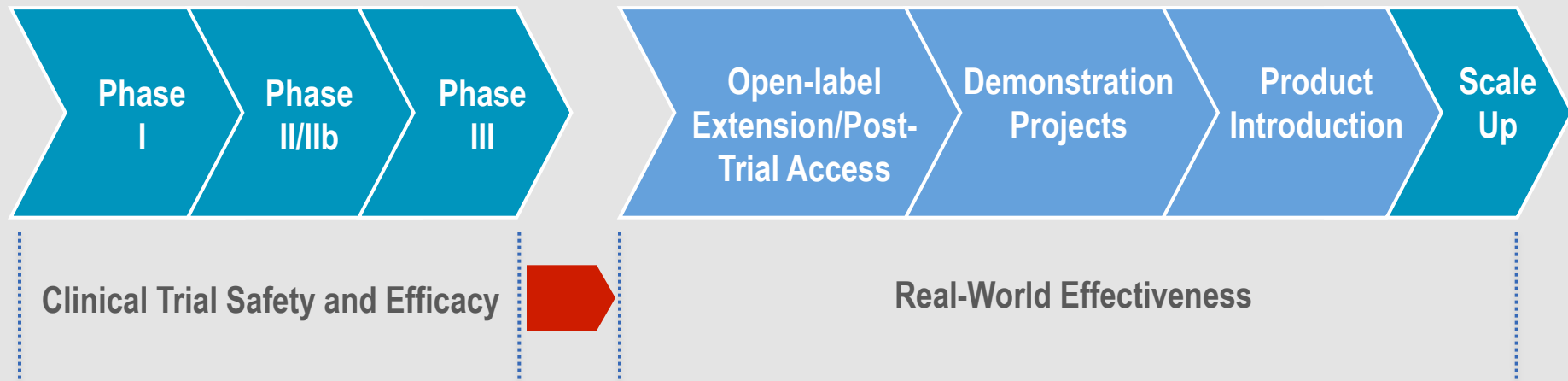
AIDS

Guidance Point 19:

Availability of Outcomes

Researchers should inform trial participants and their communities of the trial results. During the initial stages of development of a biomedical HIV prevention trial, trial sponsors and countries should agree on responsibilities and plans to make available as soon as possible any biomedical HIV preventive intervention demonstrated to be safe and effective, along with other knowledge and benefits helping to strengthen HIV prevention, to all participants in the trials in which it was tested, as well as to other populations at higher risk of HIV exposure in the country.

Research to Rollout: A schematic road map



Highlighted in darker blue are the areas where biomedical HIV prevention research has the most experience to date. The “gap” between positive effectiveness data and access for trial participants and their communities is less familiar territory – as are the steps in lighter blue.

From Research to Rollout

Post-trial access

- Intervention provided to trial participants and, sometimes, their communities, after trial & before product is available for widespread use

Open label extensions

- Intervention made available in follow-on protocol in which participants from previous RCT know they are receiving active intervention
- Gather information about how product use in people who are now aware of potential benefit

Open label/ Implementation studies

- Research protocols similar to above but enrolling new participants

Demonstration projects

- “Road test” use of new option in real-world settings – not in trial site
- Can address both infrastructure needs to deliver intervention and ways individuals integrate it into daily activities and decision making.
- Can help answer core questions about for whom and how

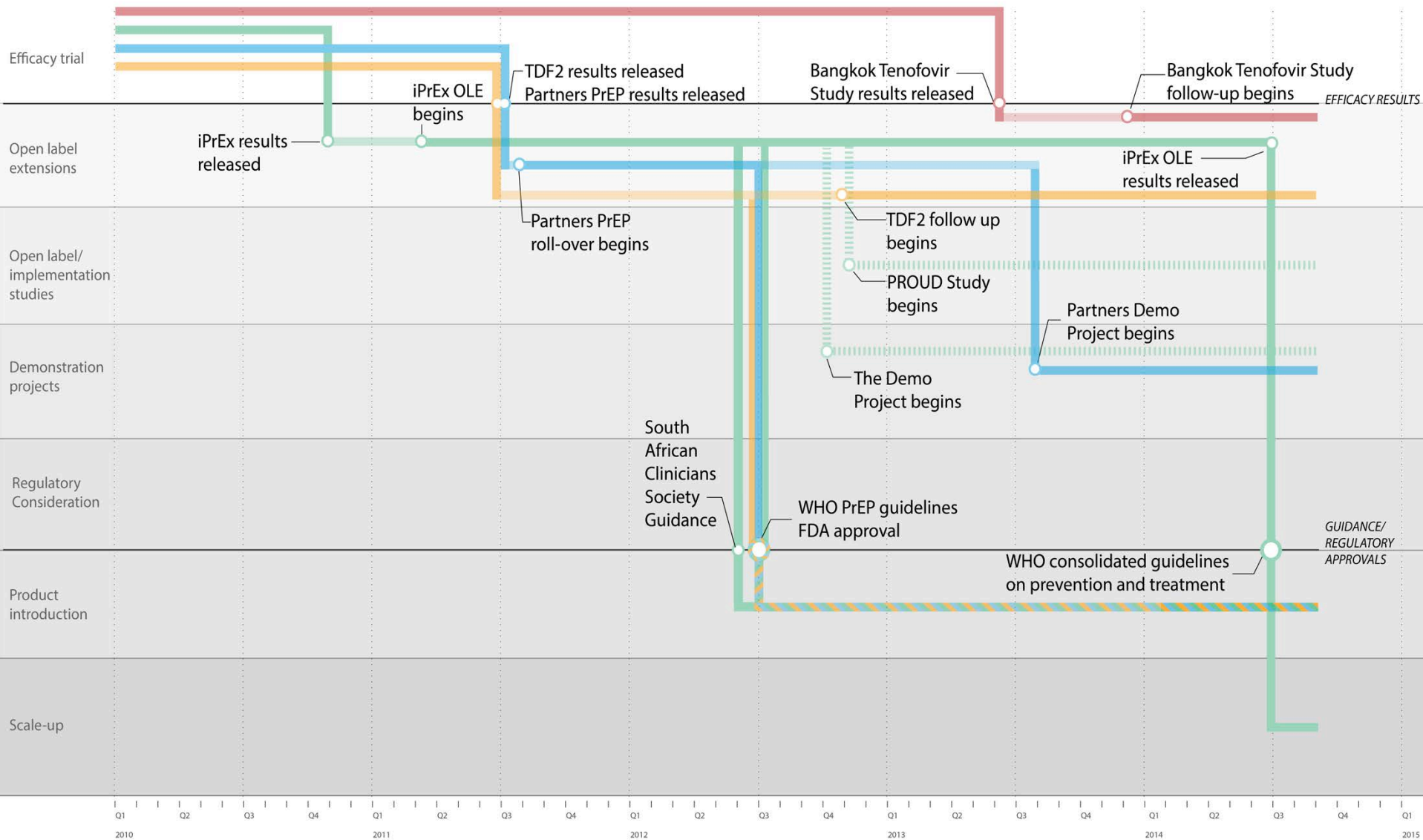
Product introduction

- Complex process of formally making new options widely available. Can include meeting regulatory requirements, WHO prequal, various country-specific requirement, logistical challenges

Scale-up

- Ramping up access to new options for all who need them – mobilization of resources for procurement, distribution, delivery, worker training and other costs associated with rollout; quick ID and resolution of bottlenecks

The Oral PrEP Experience



The Oral PrEP Experience: Peru

- Trial success leads to...
- ...successful open-label extension...
- ...but Truvada is not registered for treatment (after six years of delays)...
- ...so no clear path to next steps for prevention
- Whose responsibility is it – research group? Gilead? MOH? Trial funders?

Key Questions about Users (& Influencers)

-
- The diagram consists of a list of seven key questions on the left, followed by three blue curly braces on the right that group them into three categories. The first brace groups the first three questions under the 'Personal' category. The second brace groups the next three questions under the 'Programmatic' category. The third brace groups the last two questions under the 'Policy' category.
- Who needs what?
 - Who wants what?
 - Who gets what?
 - How to deliver it?
 - How to support adherence?
 - Who pays?
 - Who decides?
- Personal
 - Programmatic
 - Policy

The most recent bottom line(s)

- Research ethics call for maximising benefits to stakeholders who participate in research
- Local community stakeholders are to be among the first to gain access to new products should they be found safe and effective
- How trial sites communicate and interact with stakeholders about post-trial access is likely to have significant influence on community stakeholder perceptions of trial – and research enterprise at large
- Not if, but how

Thank You!



The End

- For more information
www.avac.org
- Stay tuned for the new online GPP course www.avac.org/gpp
- *AVAC Report 2013: Research & Reality* and graphics at
www.avac.org/report2013
- Sign-up for Advocates' Network:
www.avac.org/advocatesnetwork