Case Study: NIH Guidance on Post-trial Access to Antiretroviral Treatment

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The views expressed are my own and do not represent the views of the NIH, PHS, or DHHS
NIH guidance on post-trial access, 2005
Scope of guidance

Applies only to:

- Provision of antiretroviral treatment
- HIV antiretroviral treatment trials
- Developing countries
NIH expectations

- The “NIH expects investigators/contractors to address the provision of antiretroviral treatment to trial participants after their completion of the trial. The NIH recommends investigators/contractors work with host countries' authorities and other stakeholders to identify available sources of antiretroviral treatment.”
- “Priority may be given to sites where sources are identified for the provision of antiretroviral treatment following the completion of the trial.”
Justification for post-trial access

• Otherwise, “there is an increased possibility that trial participants may not receive post-trial antiretroviral treatment. This would end the benefits of treatment they received during the trial and could affect their ability to use certain antiretrovirals in the future.”
Limits to NIH support

- “The NIH is statutorily authorized to support and conduct biomedical research... In the research arena, the NIH may not support or provide services beyond its statutory authority such as providing antiretroviral treatment following the completion of a trial.”
The MULTI-OCTAVE trial
Background

- Improved access to antiretroviral therapy (ART) in many LMICs
- Many patients are now failing second-line ART regimens due to resistant HIV strains
- Third line therapy is ideally tailored to the individual patient using HIV genotyping
Trial design

- Open-label phase IV, prospective interventional, strategy study
- Enrolling 500 HIV-1-infected adults who are currently failing a second-line regimen containing a protease inhibitor
- Sites in Brazil, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda
- Sponsored by NIAID with pharmaceutical company support
Trial design

1. **Allocation to treatment cohort**
   (A, B1, B2, B3, C, D)

2. **Virologic failure**

   - **Step 2**
     - New resistance testing
     - Allocation to new treatment cohort
Hypothesis

- The availability of novel antiretroviral agents and use of contemporary management tools for selection and monitoring of third-line treatment will enable a ≥ 65% rate of successful virologic control at 48 weeks of follow-up.
Post-trial access in the MULTI-OCTAVE trial
The problem

- Some of the therapeutic agents being evaluated in the study were not available outside the trial in host countries
- Participants who needed them would leave the trial without access to these life-saving drugs
Challenges

- Obtaining the drugs
- Supplying the drugs
The solution, part 1

• The manufacturers of darunavir, etravirine, and raltegravir agreed to supply them free of charge for two years to participants who needed them at the end of the trial

• Most clinical care and other components of ART would need to be obtained elsewhere

• Two years provided window for licensing approval to be sought
The solution, part 2

- In order for drugs to be administered at study sites, they had to be part of a study...
- Step 3 added to the study:
  - Participants taking darunavir, etravirine, and raltegravir given the option of staying in study for additional 96 weeks
  - Testing how likely participants are to be virally suppressed two years after return to clinical care
The consent form
Entering Step 3

After you have completed the study ... you and your doctor will decide what treatment you should have. If continuing to take the same or similar anti-HIV drugs would be of benefit to you, the study staff will discuss how you may be able to obtain them. You may be able to obtain them outside of the study. If you are taking darunavir, raltegravir, or etravirine at the end of the study, you will be asked if you would like to enter Step 3 and get these drugs through the study for up to another 2 years.
After the study

When you finish Step 3, you will continue to get treatment and care through local programs and clinics.
The MULTI-OCTAVE trial and the ethics of post-trial access
Who is responsible?

- On-going debate about who is responsible for providing post-trial access (sponsors, researchers, national governments, global donors, ...)
- Post-trial access in MULTI-OCTAVE required collaboration between multiple parties
How long?

- On-going debate about how long post-trial care must be provided for
- The researchers negotiated two years
  - Is this sufficient?
  - Is the principle they used generalizable?
  - What if the drugs don’t get licensed in host countries?
Access to what?

- Focus of guidance has been on access to the products of research
- Optimal post-trial care required more than just antiretrovirals
Access how?

- Post-trial access is usually thought of as *post-trial*
- MULTI-OCTAVE incorporated it into a new study
  - Is this preferable?
  - Could it generate further obligations?
The challenge for guidance

- The plan for post-trial access was *consistent* with the NIH guidance
  - But how much did the guidance guide?
  - Could it guide more and still apply widely?
Post-trial Issues to consider

• Provision of the intervention
• Other health services offered during the trial
  – Scientific implications hypotheses tested
• Other resources provided during the trial
MIRA: Methods for Improving Reproductive Health in Africa: a phase III effectiveness trial of the diaphragm and lubricant gel for HIV prevention among women in Zimbabwe and South Africa.

• Participants were randomized to receive:
  – a latex diaphragm, lubricant gel, and condoms (intervention)
  
  or

  – condoms alone (control)
Provision of the intervention

• To prevent bias, all women were fitted with, and practiced using the diaphragm

• Randomization after this
  – Women in the control group promised to receive a diaphragm if efficacious results

• Scenarios development to plan for dissemination
Results over the course of the study (2003-2006)

• 151 out of 2476 women (annual incidence: 3.9%) were HIV infected in the control
• 158 out of 2472 women (annual incidence: 4.1%) were HIV infected in the intervention
• No impact!!
What we failed to consider

• Rolling recruitment meant that women exited the trial before results were final
  – Many wanted their diaphragm*
• Funder says no way!
• What did we do?

* Interim results weren’t huge
What we did

• Met with a bunch of ethicists and lawyers
• Devised a counseling strategy about unknown efficacy
• Developed a “post-test” as part of a new consent
  – IRB approval etc
OTHER RESOURCES PROVIDED DURING THE TRIAL: SCIENTIFIC IMPLICATIONS
All participants (both arms) received:

- Risk reduction counseling and/or HIV education
- Condom provision & counseling
- STI treatment services
- Cervical Ca dx and tx
- Partner testing and referrals
- Case management
- PrEP?
- Circumcision?

• Far exceeds the local standard of care
• Often overlaps with the intervention package
Evaluating multi-component technologies

Intervention vs. Control

New technology + Effective prevention vs. Effective prevention

Attributable fraction
What hypothesis are we testing?

• **Not** whether diaphragms are effective given local standard of practice
  
  • **Rather**

• Are diaphragms effective over and above a comprehensive prevention practice that probably cannot be sustained after the study is over
The Ambiguity and the Exigency: Clarifying ‘Standard of Care’ Arguments in International Research

Alex John London
Carnegie Mellon University
Why Not the Status Quo?

- Investigators are responsible for the care of all participants in the trial
- Motivates control participants to enroll and be retained
- IRBs (in-country and in US) are happier with this approach
- Permits attribution to a very specific intervention
Why Not Global Best Standard?

• If it cannot be attained and sustained in the host community, research:
  – May not be relevant to the institutions or practices of the host community
  – May create problems of continuity of care / prevention post-trial

• Alters the primary study objective
Highest Attainable and Sustainable Standard

• Asks a question clearly relevant to the health-related institutions and health needs of host population
• More likely to be sustainable post-trial
• Ought to be more appealing to host communities
• Should this be a standard for selecting interventions to be tested?
• Early assumptions regarding efficacy; If it works:
  – Like adherence, people will use it
  – It will be cost effective
  – Funds will be found
OTHER RESOURCES PROVIDED DURING THE TRIAL
Bricks and mortar
Fleets of vehicles
State of the art labs/dx equipment, freezers, technicians
Human resources in-country and US
THE IMPERATIVE IS TO DO IT ALL OVER AGAIN
Post trial access: a case study

Walter Straus, M.D.
Merck Research Laboratories
Merck & Co., Inc.
• The opinions expressed are those of the author and do not necessarily reflect those of his employer.
The indinavir (CRIXIVAN™) story

• An early experience with post-trial access (PTA) - (1990’s)
• Some practical considerations
• Context within a drug development program addressing a major public health issue
• Perspectives and roles of different stakeholders, including international issues
• The events occurred years ago, but the principles remain
Background

• In the early 1990’s HIV/AIDS was increasingly recognized as the major global public health of our time
• The pandemic was rapidly progressing in several large regions of the world
• By 1995, HIV/AIDS was the leading cause of death among persons aged 25-44 years in the US
• In the US alone, there were ~1m HIV-infected persons at risk of death due to AIDS
Early HIV/AIDS treatment strategies

- Control and prevention of opportunistic infections

Introduction of drugs directly targeting HIV (through 1994)


- All are nucleoside analogues

These drugs were critical breakthroughs, but not sufficient. HIV replication decreased, but resistant strains ultimately emerged, and disease progressed.
Drug discovery and development is difficult and requires significant infrastructure and resources.

Developing a new medicine takes an average of 10–15 years; the Congressional Budget Office reports that “relatively few drugs survive the clinical trial process.”

<table>
<thead>
<tr>
<th>Stage</th>
<th>Duration</th>
<th>Volunteers</th>
<th>Compounds</th>
</tr>
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<tbody>
<tr>
<td>Drug Discovery</td>
<td>3–6 years</td>
<td>~5,000–10,000</td>
<td></td>
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<tr>
<td>Preclinical</td>
<td>~3 years</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>Clinical Trials</td>
<td>~2 years</td>
<td>5</td>
<td></td>
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<tr>
<td>FDA Review</td>
<td>42 days</td>
<td></td>
<td></td>
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<tr>
<td>Scale-Up to Mfg.</td>
<td>0.5–2 years</td>
<td>One FDA-approved</td>
<td></td>
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<tr>
<td>Post-Marketing Surveillance</td>
<td>Indefinite</td>
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Development of an antiretroviral drug (in brief)

Merck initiates AIDS program 1986

Protease described July 1988

PanAm Flt 103 bombing (Lockerbie)
Lead Merck HIV biochemist killed*

L-735,524 (indinavir) assigned number Jan 1992

~23,000 compounds screened as NNRTIs 1990-92

L-689,502 fails (toxicity) Mar 1990

L-735,524 moved into animal safety studies Jul 1992

L-735,524 600 mg synthesized for safety trial Sep 1992

Phase I trial starts Feb 1993

L-735,524 dosage increased, combination with AZT tested Feb 1994

L-735,394 (back up to 524) approved for safety studies Dec 1993

Phase II trial evaluates different dosages starts Oct 1993

Apparent resistance to indinavir in some patients on lower dosages Jan 1994

L-735,394 fails safety testing May 1994

L-735-524 Phase III "Go" decision

L-735-524 dosage increased, combination with AZT tested Feb 1994

15 step manufacturing process identified Feb 1994

Early results announced ICAAC Sep 1995; CROI Jan 30 1995

Expanded access program announced July 1995

Expanded access program announced July 1995

Accelerated NDA submitted Jan31 1996;
FDA Advisory Subcommittee recommends indinavir approval Mar 1996

Manufacturing plant initiated Mar 1995

Inter-Company Collaboration for AIDS Drug Development Apr 1993

Proof of concept study starts Jun 1993

Manufacturing plant initiated Mar 1995 (end Mar 1996)

Early results announced ICAAC Sep 1995; CROI Jan 30 1995

Expanded access program announced July 1995

Phase III initiated US, EU, Australia, Brazil - July 1995

Galambos L, Sewall JE. Confronting AIDS: science and business cross a unique frontier (Merck & Co., 1998)
Some practical issues

• Drug manufacturing and supply
  – Complex production; high dose
  – Addressing community access and clinical demand

• Late stage trials for licensure
  – Several late stage trials: US, Europe, Australia, Brazil
  – US trials conducted by Merck or AIDS Clinical Trials Group (ACTG)
  – Brazil trial conducted by Merck

• FDA and community actively encouraged drug development
  – AIDS community participated in advancing research as a public health priority; recruitment
  – Support for trials, accelerated review
Protease enzyme and indinavir

5 chiral centers
Manufacturing

**Discovery/Early Dev.**
- Pre-clinical supplies
- Very small scale (e.g. In vitro)
- Grams / months

**Pilot plant**
- Early clinical supplies
- Scale: usually (e.g. 10’s – 100’s participants)
- Multi-purpose (program)

**Manufacturing plant**
- Licensed products and (usually) late stage programs
- Built specifically for indinavir
- 1000’s – 100,000’s patients
- 250,000+ kg / year

**Challenges:**
- Unprecedented combination of complexity and demand
- “High” drug quantity required: 2.4g/day (vs. e.g. 5-10 mg/day) – implications for production
- Strong activist community pressure for early access (manufacturing site inspection)
- Pilot plan produced clinical and initial commercial supplies (implications for other programs)
- Manufacturing plant construction initiated very early

Source (old photos): Merck Archives
Post-trial access in pivotal indinavir studies

United States, Europe, Australia

- Several studies
- Different combinations of background therapy +/- indinavir in treatment-experienced patients
- Conducted by Merck or ACTG
- Existing infrastructure
- Surrogate and/or clinical endpoints
- PTA provided (open label extension with cross-over) through licensure

Brazil

- Monotherapy (indinavir or zidovudine) vs. both in treatment naïve patients
- 3rd drug added during trial (standard of care changed)
- Conducted by Merck
- Some infrastructure support provided
- Study terminated early due to efficacy (DSMB)
- Post-trial access provided through an open-label extension (with cross-over) for up to 5 years
Clinical trial site selection: Brazil

- Apart from Mectizan (river blindness) drug donation program, first major clinical trial by Merck in a “developing country” setting
- Advantages of more generalizable data vs. risks of conducting research in “non-traditional” setting
- One of first countries to prioritize HIV prevention and control
- “Developing country” with several centers of research excellence
- Effective advocacy by strong subsidiary

Post-trial access design issues

• Based on clinical considerations, not precedent

• Key factors
  – Scientific/medical value in following research participants on novel therapy over time
  – Responsibility to research participants (potential access to intervention for both study arms)
  – Access to therapy
  – Potential risks associated with therapy discontinuation
Agreements - Brazil

• Infrastructure
  – Sponsor provided some sites with laboratory support to conduct the study (e.g. flow cytometry equipment to measure CD4 cell counts)

• Responsibilities to study participants
  – Following initial study, study extension provided study drugs for up to five years total
  – Assumed drug would be licensed and accessible by then
  – Recognition that access was not widely available
Publication

- Primary results published

A CONTROLLED TRIAL OF TWO NUCLEOSIDE ANALOGUES PLUS INDINAVIR IN PERSONS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND CD4 CELL COUNTS OF 200 PER CUBIC MILLIMETER OR LESS

Scott M. Hammer, M.D., Kathleen E. Squires, M.D., Michael D. Hughes, Ph.D., Janet M. Grimes, M.S., Lisa M. Deemer, M.D., Judith S. Currier, M.D., Joseph J. Eron, Jr., M.D., Judith E. Feinberg, M.D., Henry H. Balfour, Jr., M.D., Lawrence R. Deyton, M.D., Jeffrey A. Chodakewitz, M.D., and Margaret A. Fischl, M.D., for the AIDS Clinical Trials Group 320 Study Team

REV. INST. MED. TROP. S. PAULO

RANDOMIZED, DOUBLE-BLIND TRIAL COMPARING INDINAVIR ALONE, ZIDOVUDINE ALONE AND INDINAVIR PLUS ZIDOVUDINE IN ANTIRETROVIRAL THERAPY-NAIVE HIV-INFECTED INDIVIDUALS WITH CD4 CELL COUNTS BETWEEN 50 AND 250/MM3


- Secondary analyses (extension studies) were difficult to publish
Key observations

• Post-trial access program considerations varied by country

• Conducting post-trial access program within a study setting provided assurance that safety data would be reliably captured

• Multi-stakeholder involvement was critical to successful PTA design and implementation

• Company prioritization, and good fortune favored rapid development

• √ Treatment made available for ≥2 years following trial completion
  (Standard of care meets WHO guidelines)
• √ Treatment failure preferentially based on clinical criteria
• √ Use of generic drugs not advised
• √ Treatment of family members need not be defined as responsibility of sponsors
• √ PTA period should advance continuing research
• √ Locate studies preferentially in countries with national treatment programs
• √ Less intensive strategies in PTA than in clinical development
• Pre-study contract should detail all responsibilities and demarcations for PTA
• (IAS-ILF should disseminates its recommendations and facilitate implementation)

End
• 1981 1\textsuperscript{st} cases of unusual syndrome described in young males
• 1982 – AIDS defined
• 1984 – HIV identified as causative agent
• 1987 – Global Programme on AIDS (WHO)
• 1988 – HHS mails AIDS information to 107m US households (right)
Post-Trial Responsibilities Conference: Ethics and Implementation

Session III: Lessons Learned, Industry Case #2

Laurie Letvak, M.D.
VP, Head, Clinical Development Policy
Opinions expressed during this talk and in the panel discussion are those of the speaker and do not necessarily represent the views of Novartis Pharmaceuticals Corporation.
Agenda

1. Overview of considerations in provision of drug to patients following clinical trials

2. Cases
   - Gleevec® (imatinib mesylate) in CML
   - Drug X – marketed drug studied in unapproved indication

Gleevec is a trademark of Novartis AG
Overview of considerations for post-trial access

- Marketed vs not yet approved for any indication
  - Marketed for different indication vs marketed for study indication
  - Marketed drug has drug supply/manufacturing capacity. Drug supply may be issue if unanticipated demand

- Global development program – global strategic approach desirable for drug access, but implementation may vary in different geographies based on local regulation and laws

- For patients on drug/placebo – are there alternative therapies available? Is the condition serious/life-threatening?

- How long should therapy be provided? What data collection is needed at the start? Over time?

- What other elements of care should be the responsibility of the company?
Considerations for post-trial access

- Post-trial access to be addressed in protocol, ICF as per Declaration of Helsinki, but specifics not necessarily stated

- When planning the “parent protocol”, ideally needs for different scenarios should be considered
  - Need for additional safety/efficacy data following primary data analysis, key secondary analyses and potential filing/approval
  - Contingencies if trial stopped early (for either overwhelming efficacy, futility)
  - Provision for patients not originally randomized to investigational agent (where cross-over not already in place)
Potential Options for Post-trial Access (1)

- **Built-in Study Extension (already included in parent protocol):**
  - Patients may continue on study until they meet discontinuation criteria – specific duration or clinically defined event
  - May include reduced schedule of assessments per standard of care.
  - May revert to local labs, single ECG’s
  - Data collection for Treatment, safety, reasons for discontinuation required as minimum

- **Extension Study**
  - Unique protocol, study number which allows patients from one or more studies in one indication only to receive treatment after completion of primary analysis

- **Protocol Amendment**
  - In cases where extension not anticipated or other changes in protocol required to implement (could be based on study results or other changes in medical practice)
Potential Options for Post-trial Access (2)

- **Roll-over Study/Basket Protocol**
  - Allows patients from multiple protocols or multiple indications within a program to be treated after completion of parent studies, allowing for closure of all parent protocols
  - Option for patients who are assessed by investigator to benefit from continuing ongoing treatment (individual “benefit-risk” assessment)
  - Safety Data Collected

- **Not generally intended for trial patients:**
  - Expanded access
  - Compassionate use
  - Individual named patient protocols
Case 1:
Gleevec® in Chronic Myeloid Leukemia
Gleevec® - CML registration program

- Initial trial – proof of concept for targeted molecular therapy, prolonged survival in pts with dire prognosis not anticipated

- Ph I study (3 US sites) began 1998, with almost all pts responding after initial very low dose cohorts. Study extended, and drug supply assured.

- Initial informed consents for Ph I and II studies did not explicitly address ongoing drug supply. Company chairman committed that study patients would receive drug “for life”

- 1999 - Ph II registration studies initiated.
  - Study 109 – 293 pts with AP (accelerated phase) CML
  - Study 102 – 260 pts with BC (blast crisis)
  - Study 110 – 532 pts with late CP (chronic phase) – either failed or intolerant to IFN-α
With commercial drug available many patients chose to receive drug commercially with local physicians.

Following Ph II study extensions, roll-over protocol available
- Consent stated they could receive drug in study as long as investigator felt they were continuing to benefit

Study 109 AP
- 293 pts started core; end of core mid-2002 76 pts enrolled on extension, 42 pts enrolled in further extension in 2004. 7 completed the extension and 6 transitioned to roll-over protocol, the other receives commercial drug. Last patient completed Sept 2013.

Study 102 BC
- 293 on core, 8 pts ongoing as of July 2004. 7 discontinued during follow-up and one remaining pt went on rollover and completed treatment in 2013.

Study 110 CP
- 532 on core 1999, 486 pts enrolled on extension #1 in 2001, 307 continued on #2 in 2004. 81 completed extension and 74 continued to rollover study. 7 pts in Germany on commercial drug. Last pt completed Nov 2013.
Ph III 106 (IRIS) trial initiated in patients with early CP – 1106 pts randomized to either imatinib or IFN-α. Most IFN pts either crossed over to imatinib or d/c’d study to receive commercial drug.

Core study amended in order to permit data collection/publication of landmark study. Study concluded 2012, 13 years after the start.
- 402 pts still on study drug, 449 known to be alive.

IRIS country transition plans:
- Most pts transitioned to roll-over study – could stay on as long as they benefited.
- Some moved to commercial drug under insurance coverage.
- Some received drug via Patient assistance programs.
Case 2:
Drug X in life-threatening disease
(drug is marketed for other indication)
Marketed Drug X being investigated in separate life-threatening indication (1)

- Pre-clinical data supported a small pilot trial of 6 months of treatment followed by long-term extension

- Based on encouraging data, 200 pts randomized Ph III trial done, followed by 3 year extension (140 pts entered extension)

- Drug-drug interaction study also performed in parallel, with extension

- Global registration filings made, but company asked to provide more data to support approval. Company decision made not to further pursue additional trial/indication

- 99 patients remained on extension studies, felt to be benefitting from therapy (10 countries)

- Several potential solutions considered in order to find pragmatic way forward
Marketed Drug X being investigated in separate life-threatening indication (2)

- All countries except UK (5 patients) and Canada (1 patient) required clinical protocol to continue to provide drug in unapproved indication.

- Roll-over study, incorporating multiple studies, one indication, seems to be pragmatic.
  - No further efficacy data collection required
  - Safety data/SAE’s to be collected
  - Allows closure of parent studies
  - Global protocol can be implemented at local level (cost, logistics, local regulations)

- Costs would be manageable for all countries except for Japan due to MHLW requirement to supply all patient’s drugs for that indication

- Regulators of one European country did not approve roll-over study

- Other countries implemented the roll-over study or other local solutions consistent with laws and regulations
Final thoughts

- Proactive planning and anticipation of a variety of scenarios best approach
- Extent of data collection and study procedures needs to be considered and adapted over time
- Need to communicate and align expectations of all stakeholders
- Consider local regulations/limitations in planning and solutions
- Provision for drug supply following core studies and particularly when additional data no longer required, requires partnership and commitment on the part of multiple stakeholders
Thank You!

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