Streamlining Regulatory Issues: Challenges from Recent International Trials

Jim Neaton
University of Minnesota

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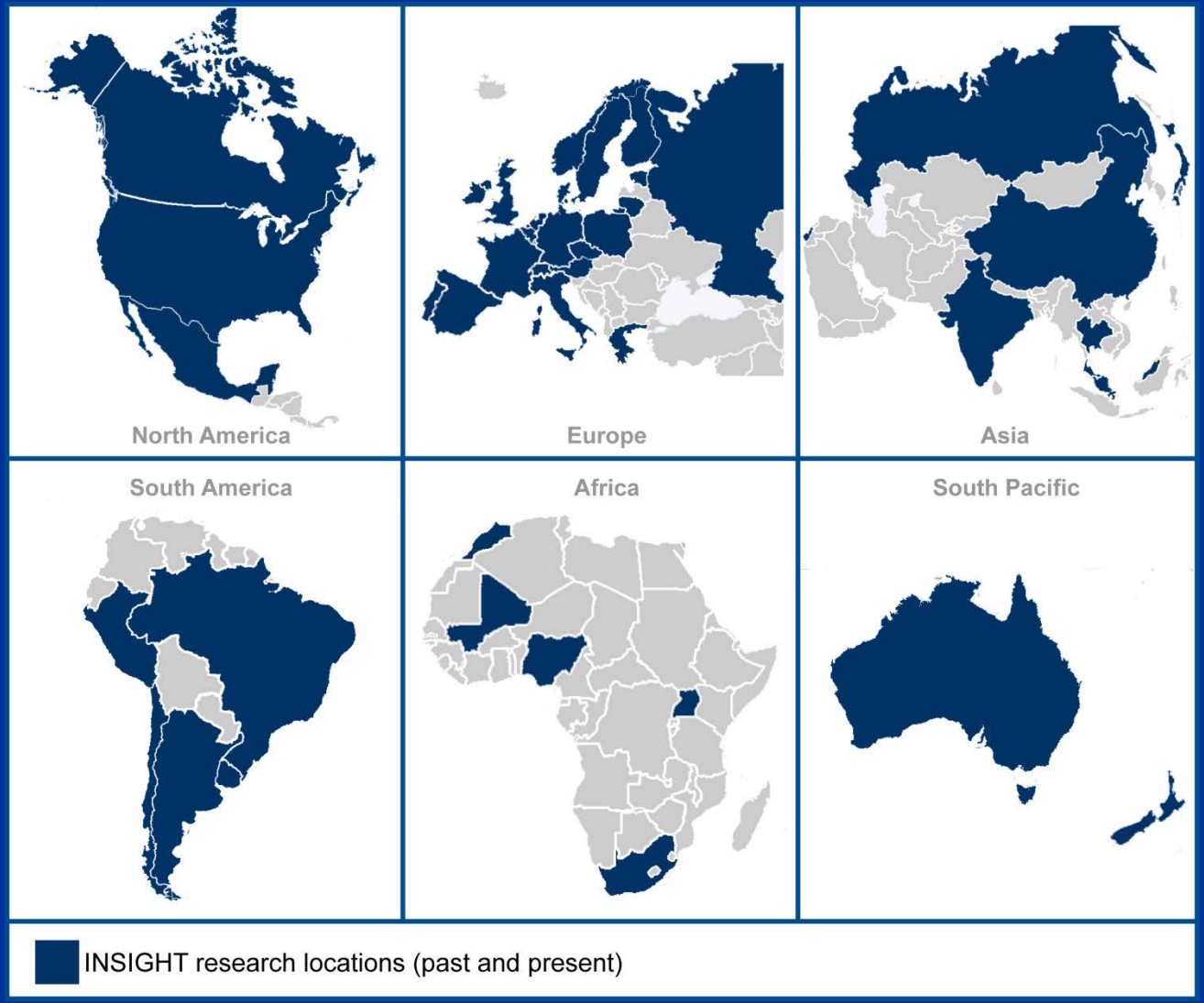
Outline

- Case examples of challenges from HIV trials conducted by NIH-funded INSIGHT clinical trials network.

- Three recommendations

International Network for Strategic Initiatives in Global HIV Trial



NIH is primary funder.

Challenges Resulting from Conflicting International and US Regulations

- Conflict with US regulations
  - Continuing Review (CR) – local international requirements allow for annual IRB continuing review by the IRB Chair (or select members), but not by the convened IRB as required by 45 CFR 46
  - Requirement for Federalwide Assurances for studies jointly funded by NIH and other governments

- Conflict with the EU Clinical Trial Directive
  - Indemnification - NIH cannot serve as a sponsor for trials in the EU requiring NIH to indemnify

Clinical Trials 2010; 7:705-718 and Editorial 622-625.

Continuing Review of Protocols

- The U.S. Office of Human Research Protections (OHRP) oversees research supported by the U.S. Department of Health and Human Services.

- OHRP regulations require an annual review of each research protocol by the majority of IRB/EC members (regulations apply to foreign countries if they receive federal support).

- Other countries do not require full-board reviews of each protocol annually.

Exemption Requested by UK

- Chair of central ethics committee reviews the protocol annually.
- Enrollment in trial halted for 3-4 months.
- Restriction lifted but "…to date, the Secretary has not made any determinations that other procedures provide equivalent protections".
- A revision to Common Rule recently proposed by U.S. Office of Management and Budget Working Group would relax continuing review requirements for some studies but may not impact problem described here.

Federalwide Assurance Requirement

- Agence Nationale de Recherches sur le SIDA et les Heptatites Virales (ANRS) in France supports 12 sites for conduct of trial but patients are centrally randomized by a NIH-funded coordinating center.

- Solution: Randomization implemented by group without NIH funds using common algorithm

EU Guidance on Sponsorship

- Sponsor must provide the insurance or indemnity to cover the liability of the investigator and sponsor.
- Variable implementation of this requirement by EU Member States.
- In most cases, the sponsor is the funder.

Sponsorship

- As funder, NIH is usually legal sponsor of trial.
- After a year of planning for a 4,000 patient international trial, NIH Counsel determined (citing Anti-Deficiency Act) in July 2008 that NIH could not sponsor the trial due to insurance and indemnification requirements of the EU Directive.
- NIH notifies U of M they will fund but not sponsor the trial. Some, but not all EU countries, designated the study as a trial of an investigational medicinal product (IMP),
- After much deliberation, U of M assumes role as sponsor

Strategic Timing of AntiRetroviral Treatment (START)

HIV-infected individuals who are ART-naïve with CD4+ count > 500 cells/mm^3

Early ART Group

Initiate ART immediately following randomization

N=2000

Deferred ART Group

Defer ART until the CD4+ count declines to < 350 cells/mm^3 or AIDS develops

N=2000

This is not a trial of a specific drug or combination of drugs. Any 1st line ART drug may be used; 1st line drugs donated by 6 pharma companies.

Implications of UM Sponsorship

- Clinical trial agreements had to be negotiated with six pharmaceutical companies donating drug by U of M instead of NIH.
- Additional insurance had to be purchased by U of M.
- A plan for managing institutional conflict of interest concerning abacavir (for which U of M receives royalties) had to be approved by Board of Regents.
- Initiation of the trial was significantly delayed.

Other Areas to Target for Harmonization and Simplification

- Insurance
- Drug importation/distribution
- Consent for stored specimens

Insurance Requirments for START by Country

Country	Limit per claim	Limit per study
Austria	EUR 1,500,000	EUR 1,500,000
Belgium	EUR 500,000	EUR 5,000,000
Czech Republic	EUR 5,000,000	EUR 5,000,000
Denmark	EUR 5,000,000	EUR 5,000,000
Estonia	EUR 5,000,000	EUR 5,000,000
Finland	EUR 5,000,000	EUR 5,000,000
Greece	EUR 200,000	EUR 9,000,000
Italy	EUR1,500,00	EUR 5,000,000
Poland	EUR 1,000,000	EUR1,000,000
Spain	EUR 500,000	EUR 2,500,000
Switzerland	CHF1,200,000	CHF 10,000,000

START Insurance Costs

- European countries $444,141

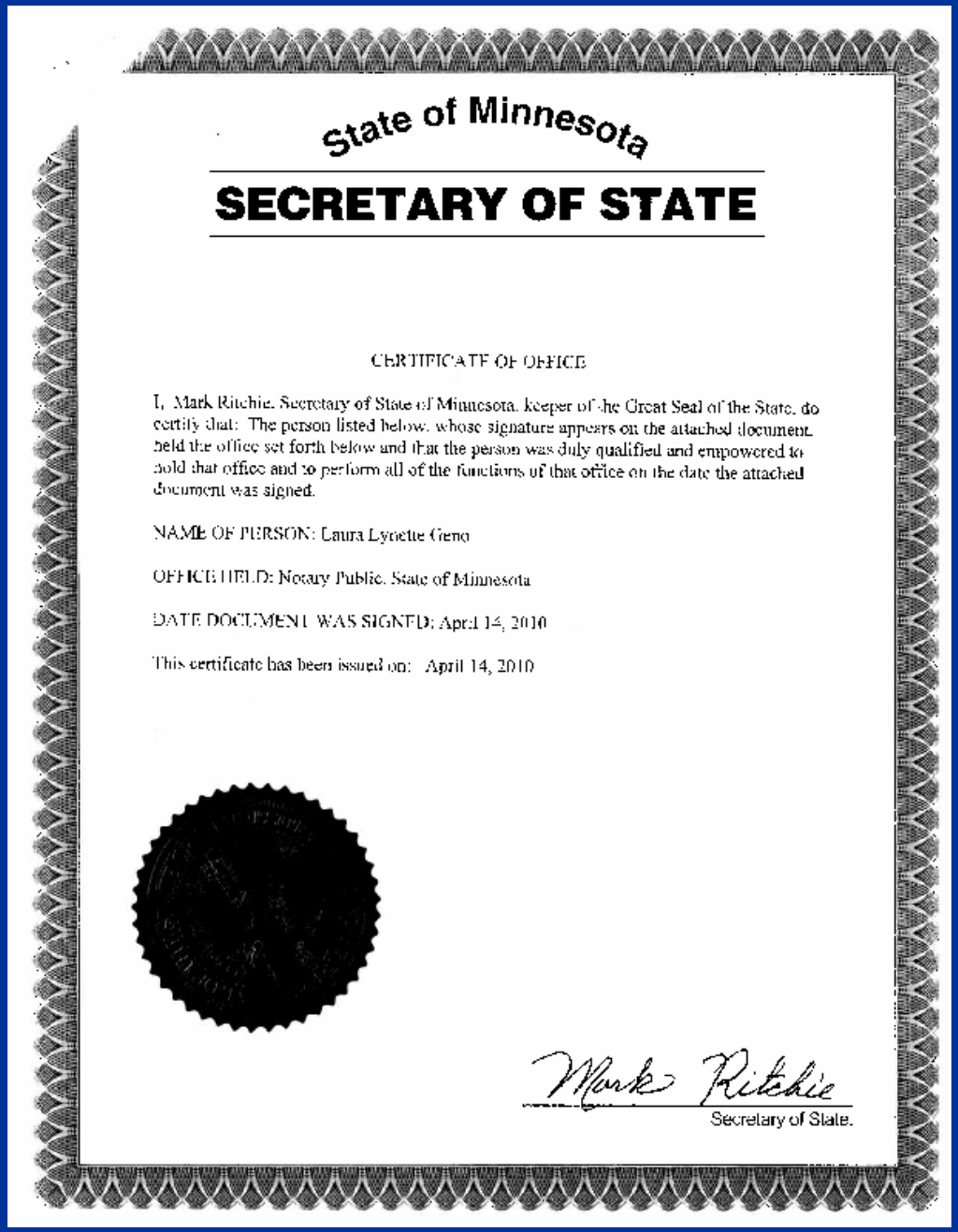
- U of Minnesota
  - To date $160,651
  - Projected total $480,000

Informed Consent Template

WHAT IF YOU ARE INJURED?

If you are injured because of being in this study, {*Insert the name of the clinic*] will give you immediate necessary treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. You will then be told where you may receive additional treatment for your injuries. There is no program for monetary compensation. You do not give up any of your legal rights by signing this form.

Certification Steps for Donated Drug to be Shipped to Chile – Step 2



State of Minnesota

SECRETARY OF STATE

CERTIFICATE OF OFFICE

I, Mark Ritchie, Secretary of State of Minnesota, keeper of the Great Seal of the State, do certify that: The person listed below, whose signature appears on the attached document, held the office set forth below and that the person was duly qualified and empowered to hold that office and to perform all of the functions of that office on the date the attached document was signed.

NAME OF PERSON: Laura Lynette Geno

OFFICE HELD: Notary Public, State of Minnesota

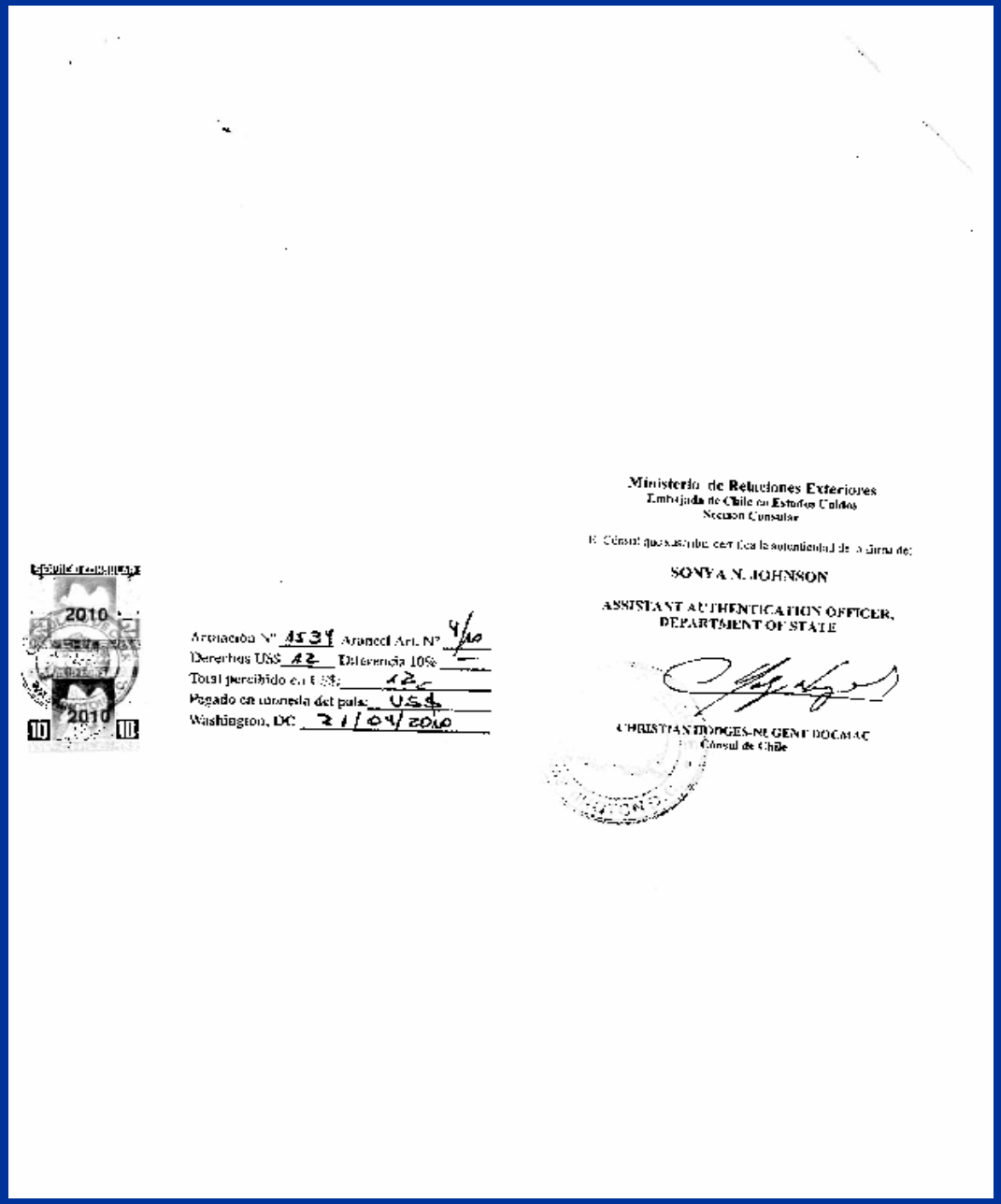
DATE DOCUMENT WAS SIGNED: April 14, 2010

This certificate has been issued on: April 14, 2010

Mark Ritchie

Secretary of State

Certification Steps for Donated Drug to be Shipped to Chile – Step 3



Ministerio de Relaciones Exteriores
Embajada de Chile en Estados Unidos
Seccion Consular

El Cónsul que suscribe certifica la autenticidad de la firma de:

SONYA N. JOHNSON

ASSISTANT AUTHENTICATION OFFICER,
DEPARTMENT OF STATE

CHRISTIAN DODGES-NUGENT DOCMAC
Cónsul de Chile

Arancel N° 4534 Arancel Art. N° 4/10
Derechos US$ 12 Diferencia 10% —
Total percibido en US$: 12
Pagado en moneda del país: US$
Washington, DC 21/04/2010

Certification Steps for Donated Drug to be Shipped to Chile – Step 4

10021181-2

United States of America

DEPARTMENT OF STATE

To all to whom these presents shall come, Greetings:

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**For the contents of the annexed document, the Department assumes no responsibility*
This certificate is not valid if it is removed or altered in any way whatsoever

In testimony whereof, I, Hillary Rodham Clinton, Secretary of State, have hereunto caused the seal of the Department of State to be affixed and my name subscribed by the Assistant Authentication Officer, of the said Department, at the city of Washington, in the District of Columbia, this sixteenth day of April, 2010.

Secretary of State

By

Assistant Authentication Officer,
Department of State

Issued pursuant to CHAN; State of Sept. 15, 1789, 1 Stat. 68-69; 22 USC 2657; 22USC 2651a; 5 USC 301; 28 USC 1733 et. seq.; 8 USC 1443(f), 8USC 44 Federal Rules of Civil Procedure

Consent for Stored Specimens

- Open-ended one time consent and blanket approval versus specific use approval
- Time duration of storage (e.g., re-approval for longer than 5 years storage)
- This is different than revised U.S. regulations being considered for “left-over” specimens.

Recommendations

- Harmonize regulations to encourage, not discourage, shared funding of multi-national trials.
- Establish procedures that permit delegation of responsibilities to multiple trial sponsors/funders
- Develop a database by country on factors that increase cost of multi-national trials:
  - Insurance requirements
  - Stored specimen requirements
  - Drug importation

Summary

- The possibilities for international collaboration are growing – it's fun most of the time, but could be better.

- Most regulations for clinical research were developed by national groups and global collaborations were not considered – that needs to change.