Forum for Collaborative HIV Research

Standardization and Clinical Relevance of HIV Drug Resistance Testing
Collaboration to Provide Access to the RESIST Datasets

Request for Proposals

I. SUMMARY

We are launching a new collaboration with Boehringer Ingelheim to allow access to the RESIST datasets. Academic and government collaborators are invited to submit proposals for analysis for review by the FCHR HIV Drug Resistance Project Review Committee. If approved, Collaborators will have access to the RESIST Datasets as described in Appendix A. All results obtained by Collaborators will be reviewed by the FCHR Review Committee and a publication plan developed jointly between Collaborators and the FCHR Review Committee. This project is a first step in generating a new model for advancing the field of interpretation of complex and highly dimensional datasets, benefiting the drug development, drug regulation, clinical research and clinical application sectors within the HIV community.

II. INTRODUCTION

The Forum for Collaborative HIV Research (The Forum) is an independent public private partnership that includes governmental agencies charged with research and with drug regulation, pharmaceutical and diagnostic companies, academic researchers and research networks, HIV care providers, HIV patient community representatives and payors, with the mission to enhance and facilitate HIV research.

The **Standardization and Clinical Relevance of HIV Drug Resistance** project was initiated in April 2002 in response to the need for developing more clarity in the field of drug resistance, both from the clinical care and the drug regulatory perspective.

The goals of the Drug Resistance Working Group are:

- To collaborate in an ongoing process with industry and regulatory agencies for the purpose of consistent application of drug susceptibility information in drug development and drug labeling
- To improve patient therapeutic management through better understanding and use of drug resistance test information

The objectives of the overall project are:

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- Identify clinical databases suitable for the generation of genotypic algorithms and phenotypic cut-offs
- Develop analytic approaches for the derivation of virologic response associated definitions of resistance for each antiretroviral drug
- Establish collaboration amongst the various constituencies to facilitate the performance of the required analyses
- Review current regulatory aspects related to standardization and quality assurance including laboratory as well as genotype interpretation issues
- Present and publish the overall findings to the relevant government drug and technology approval agencies (FDA and EMEA)
- Make recommendations for how best to establish a continuous and long-term evaluation of clinically defined HIV drug resistance

Phase 1: Genotypic algorithms for abacavir and didanosine

The Drug Resistance Working Group developed a standardized data analysis plan approved by all members, gathered data from 17 sources (including publicly funded trials and cohorts as well as industry held databases) resulting in a database of 1,230 patients for the abacavir analysis and 1,450 patients for the didanosine analysis and secured access to publicly available and proprietary algorithms allowing the first phase of the project to be completed.

The key findings of these analyses were presented at the International Workshop on HIV Drug Resistance in 2005 and 2006, and published in several peer-reviewed publications[1-4]

Phase 2: Comparison of quantitative methods

An effort led by Victor DeGruttola focuses on developing a framework in which to understand the connections between and compare the properties of the different methods, such as decision trees, neural networks, permutation tests, and resampling and bootstraps methods. This work has resulted in several peer-reviewed publications[5-7] .

Phase 3: Relating genotypic and phenotypic resistance information to virologic response to protease inhibitors containing regimen based on industry sponsored randomized clinical trials.

Members of the Forum Resistance Working Group agreed that virologic response to protease inhibitors should be the focus of the next collaborative analysis. This new activity forms the basis of our current RFP.

IV. REQUEST FOR RESEARCH PROPOSALS

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We are initiating this phase of the program by making available data from the RESIST datasets, as part of a collaborative agreement with Boehringer-Ingelheim**.** The advantages of this approach include homogeneity of high quality data, randomization of patients to a treatment arm and eliminating potential error and incompatibility due to integrating datasets from many different sources. Furthermore, this approach answers the call for greater availability of pharmaceutical sponsor datasets to academic investigators. While it is clear that release of such datasets prior to drug approval is not feasible, making them available post marketing approval has the potential to contribute significantly to our understanding of drug resistance development and its consequences.

The availability of the RESIST Dataset to academic or government mathematical and clinical experts under the auspices of the Forum for Collaborative HIV Research HIV Drug Resistance Working Group would be, to our knowledge, the first example of such a public-private collaborative approach to improving our understanding and interpretation of drug resistance and its consequences. This is an opportunity to generate a new model for advancing the field of interpretation of complex and highly dimensional datasets, benefiting the drug development, drug regulation, clinical research and clinical application sectors within the HIV community. This approach would also be a good model for other viral diseases and their treatment, such as Hepatitis C.

Collaboration will be contingent on approval of the proposed analysis by the FCHR review committee and signed agreements to adhere to the collaborative plan. All results obtained by Collaborators will be reviewed by the FCHR Review Committee and a publication plan developed jointly between Collaborators and the FCHR Review Committee.

Interested parties should submit a proposal to the Review Committee, using the specified proposal form (Appendix B). Data access will be provided following the recommendations of the Review Committee and receipt of a signed agreement form (Appendix C).

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References

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3. Assoumou L, Houssaini A, Costagliola D, Flandre P. **Relative contributions of baseline patient characteristics and the choice of statistical methods to the variability of genotypic resistance scores: the example of didanosine**. *J Antimicrob Chemother*,65:752-760.
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5. Healy BC, DeGruttola VG, Hu C. **Accommodating uncertainty in a tree set for function estimation**. *Stat Appl Genet Mol Biol* 2008,7:Article5.
6. Schumi J, Degruttola V. **Resampling-based analyses of the effects of combinations of HIV genetic mutations on drug susceptibility**. *Stat Med* 2008,27:4740-4757.
7. Yang Y, Degruttola V. **Resampling-based multiple testing methods with covariate adjustment: application to investigation of antiretroviral drug susceptibility**. *Biometrics* 2008,64:329-336.

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