

University of Colorado Health Sciences Center

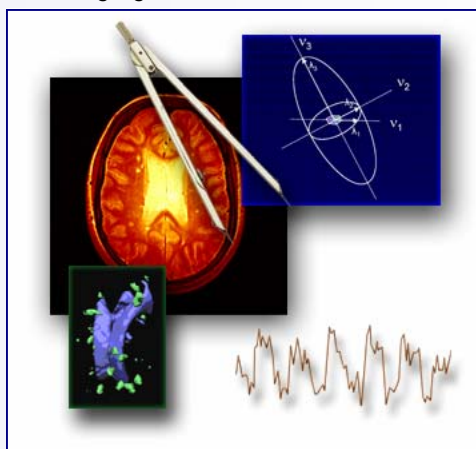
Bio-Imaging Research Laboratory (UC BIRL)

Radiology Support Services for Industry and Government

OVERVIEW

For over 18 years the University of Colorado Bio-Imaging Research Laboratory (UC BIRL) has provided image analysis and radiology review services for all clinical phases of drug development, ranging from small Phase I studies to large, international trials. Our services have been instrumental in bringing new compounds to market, particularly in multiple sclerosis and the approval of Avonex™.

The lab is composed of GCP and HIPAA trained professionals who have extensive training and experience in radiology, medical physics, computer science and clinical trials management.



- fMRI
- Magnetization Transfer
- Diffusion Tensor Imaging
- Perfusion
- Spectroscopy

HIPAA COMPLIANT IMAGE ARCHIVING

Validated 3rd party and proprietary software packages allow UC BIRL to electronically receive, QA, process, and archive medical image data in a secure, compliant manner. UC BIRL supports both film and digital data, with the ability to convert between the two. However, fully digital (filmless) studies are the preferred.

Typical analyses include lesion counting and volumetrics, focal or

whole-brain atrophy measures, serial registration, RECIST evaluation, etc. The laboratory also has the ability to process more complicated acquisitions, including diffusion tensor imaging (DTI), magnetization-transfer (MTR), and functional imaging (fMRI) using BOLD contrast. Custom data analysis for new or emerging biomarkers is available.

UC BIRL also partners with RadScience, a team of medical physicists providing education, due diligence and audit support, protocol development, image quality control, radiation dosimetry and risk analysis services. RadScience's comprehensive physics support ensures your imaging study is scientifically grounded and that subject risks are understood and mitigated.

SERVICES

UC BIRL offers a comprehensive list of services to aid industry and government sponsors in their clinical investigations.

PROTOCOL DESIGN

- Selection of Relevant Imaging Biomarkers
- Determination of Sample Size
- Imaging Intervals
- Image Acquisition Parameters

SITE SELECTION AND TRAINING

INTERNATIONAL SITE / PROJECT MANAGEMENT

IMAGE QUALITY ASSURANCE

CENTRALIZED IMAGE REVIEW AND ANALYSIS

- Radiologist Review
- Lesion Tracking
- Volumetrics (Lesion, Brain Atrophy, etc.)
- RECIST Evaluation

KEY PERSONNEL

Founder

UC BIRL was founded by Jack H. Simon MD, Ph.D., former Professor of Radiology, Neurology and

Neurosurgery at the University of Colorado at Denver Health Sciences Center (UCDHSC). He is currently the Chief of Imaging Services at the Portland VA Medical Center in Portland, OR. Dr. Simon has been involved in MS Trials including design, implementation, performance, final analyses, regulatory presentations since the mid-1980's, and has participated as a member of multiple MS Trial Advisory Boards, DSMBs, MS trial and grant reviews for the US National MS Society, the Canadian and Italian MS Societies, and has participated with European MS investigators in various academic programs and MAGNIMS sponsored MS programs and events.

Dr. Simon has acted as independent consultant for more than a dozen pharmaceutical companies involved in MS drug development, and has authored more than 120 peer reviewed scientific papers, books, chapters and reviews, the vast majority related to imaging MS and MS Clinical trials. He is a member of numerous National and International MS committees (e.g. Sylvia Lawry Center for MS Research-International MS Database, MRI committee). Dr. Simon leads and co-chairs initiatives in MRI standardization at the National and International level (e.g. Chair, session on Standardized MRI guidelines, Consortium of MS Centers, San Diego, June 2003).

Dr. Simon continues to collaborate with UC BIRL, recently forming a sister laboratory in Portland dedicated to MS research, the Oregon Brain Imaging Research Laboratory (O'BIRL).

Director

David Miller, Ph.D., is a medical physicist and Associate Professor of Radiology at UCDHSC with over ten years research and clinical experience in medical imaging and data analysis. His clinical trials experience spans CNS disease, oncology, lupus and cystic fibrosis. Having a background in both industry and academics, he has directed the image analysis and data management efforts for all clinical phases of

drug development.

As a medical physicist he also provides support for nuclear medicine (SPECT, PET-CT) and serves as an Asst. Radiation Safety Officer for UCDHSC. Dr. Miller received his Ph.D. in Nuclear Science and Engineering from Rensselaer Polytechnic Institute in 1996 and a Masters in Medical Physics from the University of Colorado Health Sciences Center in 2001.

Clinical Director

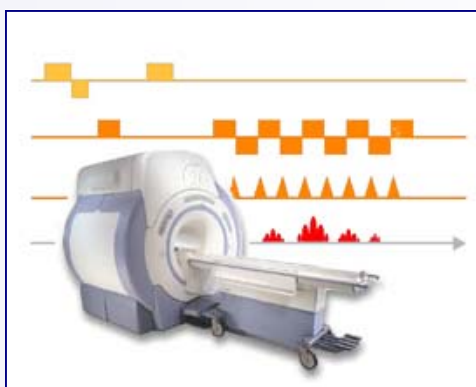
David Rubinstein, M.D., is a neuroradiologist and Associate Professor of Radiology at UCDHSC. He has conducted radiology reviews on multiple trials and provides clinical guidance for ongoing studies. Dr. Rubinstein's expertise in radiology is augmented by his research efforts in 3D visualization, PACS and the Visible Human project. He serves as a reviewer for several prestigious scientific journals and maintains professional appointments with the Denver VA Medical Center, the Denver Health Medical Center and the Denver Museum of Natural History, Division of Collections and Research.

Project Management:

UC BIRL project management staff have over 25 years combined experience in radiology-based clinical trials. They have provided project management for all phases of drug development, including large, multi-national, multi-continent studies. Project managers work closely with sponsors and CROs to ensure adherence to timelines, while supervising teams of professional research associates that provide data analysis, image tracking and quality control. Our staff are some of the best trained in the industry and are well known to many, if not most, of the key imaging centers across the globe.

Radiology:

UC BIRL partners with radiologists with subspecialties in body imaging, MSK, neuroradiology, nuclear



medicine, mammography and interventional radiology. All radiologists involved with clinical trials are trained in HIPAA and GCP.

Radiology Technologists :

UC BIRL provides access to technologist support, particularly for MR studies. Technologists are instrumental in developing practical acquisition protocols, modifying them across equipment vendors and fielding questions from techs at other sites.

Frequently Asked Questions (FAQ)

1) What formal studies has UC BIRL provided reviews for?

The Bio-Imaging Research Laboratory has provided analyses and central review for both NIH, non-profit and industry sponsored studies. The following is a sampling of studies.

Phase I

- A phase I trial (MR as safety measure)
Sponsor confidential (as per sponsor request)

Phase II

- Ongoing phase II trial with over 2200 MR studies.
Sponsor confidential (as per sponsor request).

Phase III

- MS Collaborative Research Group Trial, Interferon-beta-1a, Biogen Inc.
(5 MS Centers in USA; > 800 MRIs)
- CHAMPS Trial, Biogen Inc.
(50 MS centers, North America; >1400 MRIs)
- IMPACT
(42 Imaging Centers, North America, Europe, Israel, Greece; >1200 MRIs)



Post-Market and Extension Studies

- Two extension studies with about 200 subjects, 200 MRIs
 - CHAMPIONS 5 year study, Biogen
 - CHAMPIONS EXT 10 year study, in progress
- 2) What is the largest study that you have reviewed at your center (i.e., how many sites/ number of MRIs read)?

The large recent trials include a 50 site European, North American, South American Trial (phase II); a 50 site North American trial (phase III); and a 30 site North American, European Trial.

3) Who would be reading/reviewing the scans?

Our standard is to have radiologists oversee all reviews. We do not have non-radiologist, non-MD readers. All image processing by research associates is under the supervision of radiologists and medical physicists.

4) How long does the review process typically take from receipt to time when you can provide data back to the Sponsor?

This is negotiable and really depends on trial design and safety requirements. One standard we have used is to have a turn-around of one week from receipt of data for certain critical or primary measures, such as enhancing lesion counts. Longer turn-arounds (30 days) are typical for more complex (e.g. volumetric) measures or reviews.

- 5) What process do you typically use for collection of medical images from all centers to ensure that all are collected and that they are collected and read in a blinded manner?

Historically we've acquired the data either directly from imaging sites or via a CRO, which assumed data collection responsibilities and then relayed the images. In both scenarios we have notification and quality control systems in place that insure efficient and complete delivery of data to our laboratory. Once received, UC BIRL archives all electronic study data in an encrypted form at a Tier I Data Storage Center. As for blinding, the use and appropriateness depends on the need for a radiologist to refer to prior studies. In other words, it depends on the disease and biomarkers in question. In all cases UC BIRL remains blinded to treatment group.

6) Do you provide any type of training/guidelines for the study centers to follow?

Yes. We design detailed training and instruction manuals accompanied by an in-person training session(s) prior to start-up, generally held at Investigator meetings but on-site if necessary. Our staff is in communication with sites throughout the trial to handle issues as they appear.

7) In what form can data be transferred at an interim analysis point or end of study? Do you keep a database and input the data, or do you provide data sheets (CRFs) for input?

Analysis results are typically provided to the sponsor as studies are processed. Results can be submitted via eCRF, paper CRF, spreadsheet, delimited text file, etc. Electronic transfers are performed in an encrypted manner. UC BIRL is flexible on the format and manner of submission and works with the sponsor to meet their data management needs.

8) What other analyses / services do you provide?

Our research program spans all imaging modalities and encompasses many disease states. Any volumetric or clinical read can be accommodated. We also support advanced imaging applications including tractography, magnetization transfer, spectroscopy, fMRI, etc. If your organization is

interested in developing or assessing a biomarker, we can provide the necessary physics, computer science and radiology support to make it happen.

In addition to offering radiology review services, UC BIRL partners with RadScience, a team of medical physicists that provides education, due diligence and audit support, radiology protocol development, radiation dosimetry and risk analysis for clinical trials. RadScience services are particularly important in maintaining consistent imaging quality across sites and in the assessment of patient dose from multi-slice CT and nuclear medicine.

As an organization with a foundation in academics, UC BIRL routinely develops scientific abstracts and publications in collaboration with sponsors. We also encourage and assist in the presentation of trial results at scientific and professional meetings.

Please address questions to:

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