Resonance Health

Be Better Informed

Core Laboratory Services for Single and Multi-Site Clinical Trials

June 2017

INTRODUCTION

Resonance Health Analysis Services Pty Ltd ('Resonance Health') is an Australian healthcare company specialising in the development and commercialisation of magnetic resonance imaging (MRI) related technologies and services. Resonance Health has extensive experience in providing objective, reproducible, and quantified imaging measurements and core laboratory services for clinical trials worldwide.

Resonance Health's expertise in the provision of imaging core lab services for pharmaceutical company clinical trials has been utilised in over 20 multicenter studies spanning 25 countries over 10 years. Imaging biomarkers are increasingly used in clinical studies providing a safe, non-invasive alternative to invasive procedures such as liver biopsy. Imaging provides an ideal solution where repeat measurements are required over the life of the study.

Resonance Health has been involved in clinical studies where imaging has been used to assist in:

- The assessment of subject inclusion or exclusion
- Supporting primary and secondary end-points demonstrating drug efficacy
- Evaluating the safety profile of a new therapy

OVERVIEW OF SERVICES

- ISO 13485 certified centralised Quantitative Image Analyses, available globally, with regulatory clearances in the US (FDA), Australia (TGA), and Europe (CE Mark):
    - **FerriScan® R2-MRI** - internationally recognised as the gold standard in liver iron concentration (LIC) measurement
    - **Cardiac T2* for Iron Assessment** - offered as a dual analysis service with FerriScan to provide more comprehensive information regarding body iron stores
    - **HepaFat-Scan® -** volumetric liver fat fraction (VLFF) for quantitative measurement of hepatic steatosis
- Quantitative Image Analysis available globally in an investigational setting:
    - **Pancreatic Fat Assessment** – quantitative assessment of pancreatic fat
    - **Visceral / Subcutaneous Fat and Organ Fat in Metabolic Disease** - quantitative assessments of visceral fat, subcutaneous fat, epicardial fat
    - **Fibrosis and Inflammation –** a combination of MRI measures to assess liver fibrosis and inflammation
    - **Liver Biopsy – Stereology Services** - quantitative assessment of hepatic steatosis of digitised biopsies using stereology
    - **Bone Marrow R2 for Iron Assessment -** provides an estimation of iron levels in the bone marrow - *approval from TGA, CE mark & FDA is expected by end of 2017*.
    - **Quantitative Iron Assessment in Other Organs -** surrogate iron measurements (R2 / R2*) in other organs including pancreas, spleen, and kidney
    - **Organ Volume Measurements** - measurements of various organs such as the liver and spleen
    - **Other** - customised imaging solutions
- Scanner verification using phantoms (in accordance with the FDA Draft Guidance Clinical Trial Imaging Endpoints Process Standard, March 2015)
- Secure 21 CFR Part 11 compliant web-based infrastructure for image transfer and reporting
- Imaging trial design consultancy
- Core Laboratory Services including project and data management

The Resonance Health team includes talented scientists, researchers, and academics from across the globe. Our specially trained MRI physicists are experts in image analysis using our patented world leading technologies, and are supported by the wider research and development team at the forefront of imaging analysis development. Resonance Health also partners with many other prestigious organisations, including government research bodies, universities, international patient organisations, and centres of excellence to develop and provide world leading solutions to the clinical and pharmaceutical communities.

IMAGING ANALYSIS SERVICES

Image data is securely transferred to Resonance Health's central ISO certified Service Centre, where it is analysed by our team of experts. Result reports are made available for download by authorised personnel.

FerriScan® R2-MRI – MRI MEASUREMENT OF LIVER IRON CONCENTRATION

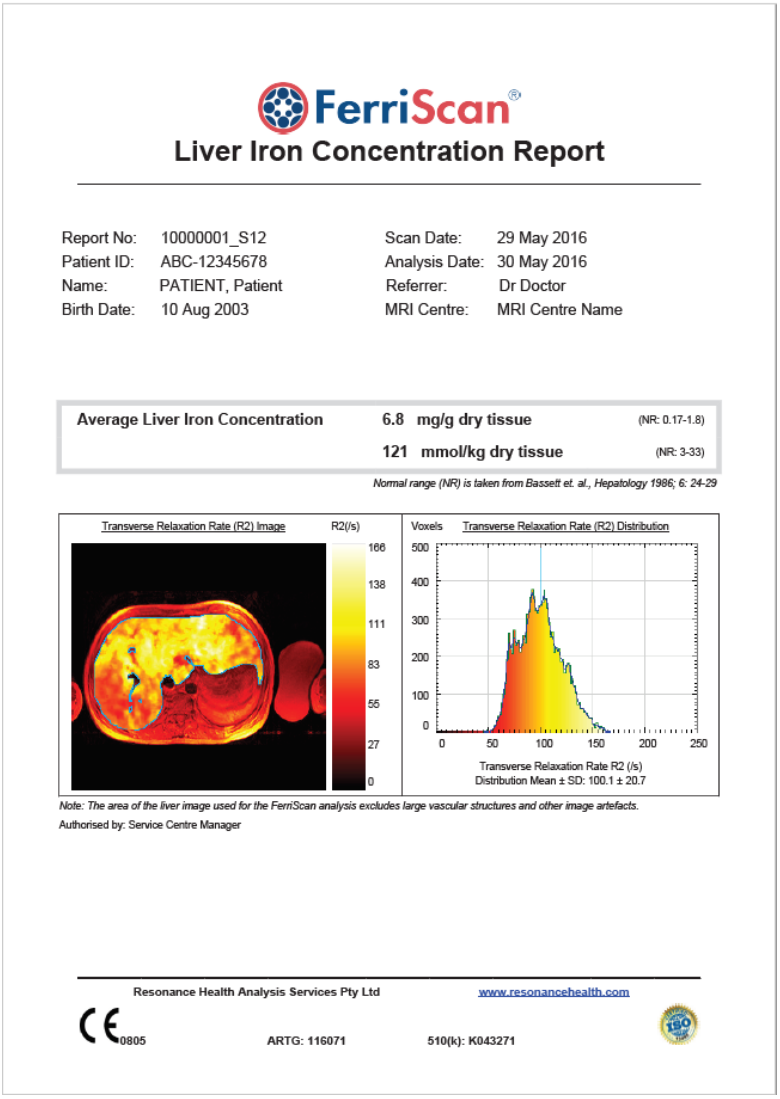
FerriScan R2-MRI is a proprietary, patent-protected imaging technology for measuring liver iron concentration (LIC) and is the first non-invasive test for LIC to have achieved regulatory clearance and approval in the US, Europe, and Australia. FerriScan is internationally recognised as the gold standard in liver iron concentration measurement.

The FerriScan service involves an approximately 10 minute MRI scan followed by off-site processing of the images in Resonance Health's ISO certified central image analysis centre to generate the LIC result. Most 1.5 Tesla MRI scanners are capable of performing the FerriScan imaging protocol. A manual is provided to each MRI Centre describing the imaging protocol in detail and the procedure for transferring image data to Resonance Health.

FerriScan offers multiple advantages over other MRI methods of obtaining LIC including:

- Extensive validation against liver biopsy across multiple centres and multiple MRI scanner makes and models from very low to very high iron levels
- The FerriScan LIC measurement is unaffected by the presence of fibrosis and fat
- A standardised approach to MRI centre set up, data acquisition, and analysis
- 'Free breathing' data acquisition suitable for paediatric patients
- FerriScan has FDA, TGA and CE Mark regulatory clearance for the measurement of LIC and is the only MRI test for LIC that gained an additional level of clearance from the FDA as a 'companion diagnostic in the NTDT setting'
- Centralised image analysis in accordance with rigorous Quality Management System standard operating procedures to ensure accuracy and reproducibility of the results
- Verification of each and every scanner using a FerriScan Phantom Pack to confirm the correct scanner configuration as an added quality control and standardisation measure:
    - A FerriScan Phantom Pack, which comprises a set of reference standards with known R2 value, is provided to each MRI Centre.
    - The Phantom Pack is scanned and image data is analysed by Resonance Health's central analysis centre.

- If successful, notification is sent to the MRI Centre that patient scanning can commence. In the event of an unsatisfactory Phantom scan, technical support will be provided detailing the required image acquisition adjustments and a re-scan will be requested.
- Performed prior to initial patient scanning for FerriScan, annually, and following any major software or hardware upgrades to a scanner.



FerriScan®

Liver Iron Concentration Report

Report No:	10000001_S12	Scan Date:	29 May 2016
Patient ID:	ABC-12345678	Analysis Date:	30 May 2016
Name:	PATIENT, Patient	Referrer:	Dr Doctor
Birth Date:	10 Aug 2003	MRI Centre:	MRI Centre Name

Average Liver Iron Concentration	**6.8 mg/g dry tissue**	(NR: 0.17-1.8)
	121 mmol/kg dry tissue	(NR: 3-33)

Normal range (NR) is taken from Bassett et. al., Hepatology 1986; 6: 24-29

Note: The area of the liver image used for the FerriScan analysis excludes large vascular structures and other image artefacts.

Authorised by: Service Centre Manager

Resonance Health Analysis Services Pty Ltd www.resonancehealth.com

CE 0805 ARTG: 116071 510(k): K043271

Sample FerriScan Report

FerriScan Sensitivity and Specificity			
LIC threshold (mg Fe/g dw)	Clinical relevance (Taken from Olivieri and Brittenham, Blood 1997; 89:739-61)	Sensitivity (95% confidence limits) %	Specificity (95% confidence limits) %
1.8	Upper 95% of normal	94% (86-97)	100% (88-100)
3.2	Suggested lower limit of optimal range for LICs for chelation therapy in transfusional iron loading	94% (85-98)	100% (91-100)
7.0	Suggested upper limit of optimal range for LICs for transfusional loading and threshold for increased risk of iron-induced complications	89% (79-95)	96% (86-99)
15	Threshold for greatly increased risk for cardiac disease and early death in patients with transfusional iron overload	85% (70-94)	92% (83-96)

Cardiac T2* – MRI ASSESSMENT OF IRON IN THE HEART

Resonance Health offers a dual analysis service including Cardiac T2* measurement in addition to a FerriScan to provide more comprehensive information regarding body iron stores. Resonance Health's Cardiac T2* analysis service has regulatory approval from the FDA in the USA, TGA in Australia, and CE mark for Europe. The Cardiac T2* analysis service is available to suitably equipped MRI Centres internationally. The imaging protocol is provided by MR equipment manufacturers and the analysis is provided at Resonance Health's central image analysis centre under its quality controlled environment.

Bone Marrow R2-MRI – MRI ASSESSMENT OF IRON IN THE BONE MARROW

Resonance Health is able to non-invasively assess bone marrow iron levels using FerriScan images. Elevated bone marrow iron in potential bone marrow transplant recipients is associated with a range of poorer health outcomes post-transplant. Quantitative assessment of bone marrow iron pre-transplant may help to predict patient prognosis and improve patient outcomes. The current gold-standard for measuring bone marrow iron is histopathological grading, which is semi-quantitative, non-standardised and subject to inter-observer error. Bone marrow R2-MRI is non-invasive, quantitative, and correlates strongly with iron in bone marrow biopsy.

Quantitative Iron Assessment in Other Organs

Resonance Health has experience in measuring surrogate iron measurements (R2 / R2*) in organs including pancreas, spleen, and kidney.

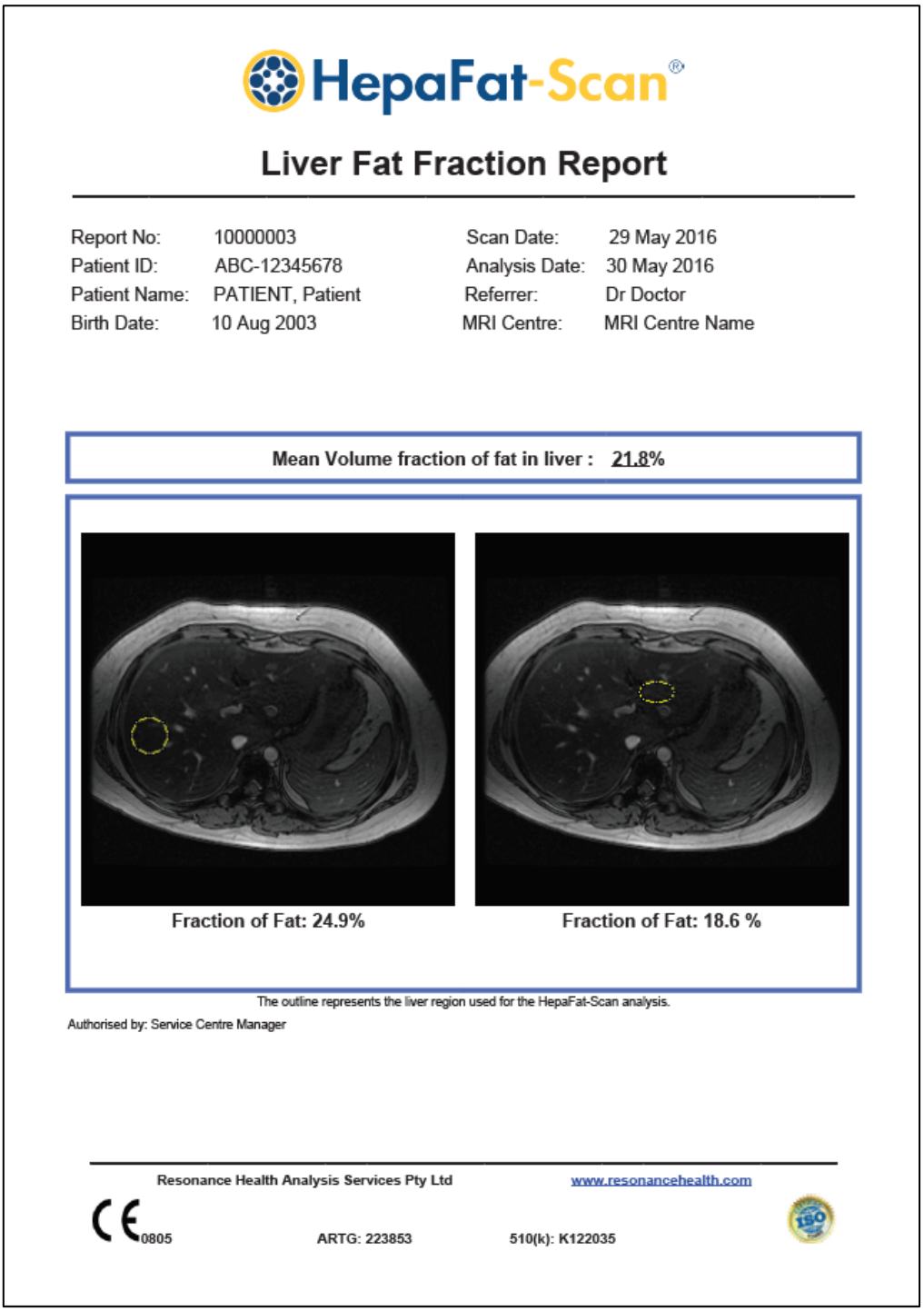
HepaFat-Scan - MRI MEASUREMENT OF VOLUMETRIC LIVER FAT FRACTION (VLFF)

HepaFat-Scan is a proprietary, patent-protected imaging technology for measuring liver steatosis and has regulatory clearance and approval for clinical use in the US, Europe, and Australia. HepaFat-Scan reports a percentage volumetric liver fat fraction (VLFF) and has been validated against liver biopsy. The HepaFat-Scan VLFF can be converted to a NASH CRN liver steatosis grading.

The HepaFat-Scan service involves an approximately 2 minute MRI scan followed by off-site processing of the images in Resonance Health's ISO certified central image analysis centre. Most 1.5 Tesla MRI scanners are capable of performing the HepaFat-Scan imaging protocol. A manual is provided to each MRI Centre describing the imaging protocol in detail and the procedure for transferring image data to Resonance Health.

HepaFat-Scan offers multiple advantages over other MRI methods:

- Validated against liver biopsy across multiple MRI scanner makes and models from very low to very high liver fat levels in non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and autoimmune hepatitis.
- Standardised approach to MRI centre set up, data acquisition, and analysis
- Single breath-hold data acquisition
- HepaFat-Scan has FDA, TGA and CE Mark regulatory clearance for the quantitative assessment of hepatic steatosis
- While standard imaging analysis utilises two (2) regions of interest (ROI), multiple ROI are available upon request
- Centralised image analysis in accordance with rigorous standard operating procedures to ensure accuracy and reproducibility of the results



HepaFat-Scan®

Liver Fat Fraction Report

Report No:	10000003	Scan Date:	29 May 2016
Patient ID:	ABC-12345678	Analysis Date:	30 May 2016
Patient Name:	PATIENT, Patient	Referrer:	Dr Doctor
Birth Date:	10 Aug 2003	MRI Centre:	MRI Centre Name

Mean Volume fraction of fat in liver : 21.8%

Fraction of Fat: 24.9%

Fraction of Fat: 18.6 %

The outline represents the liver region used for the HepaFat-Scan analysis.

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CE 0805 ARTG: 223853 510(k): K122035

Sample HepaFat-Scan Report

HepaFat-Scan Sensitivity and Specificity			
Steatosis Grades	Grade 0 vs 1 – 3 (≥5%)	Grades 0-1 vs 2-3 (≥33%)	Grades 0-2 vs 3 (≥66%)
Sensitivity (%) (95% conf interval)	96.8 (83-100)	100.0 (83-100)	100.0 (78-100)
Specificity (%) (95% conf interval)	96.0 (80-100)	94.4 (81-99)	87.8 (74-96)
AUROC (standard error)	0.963 (0.032)	0.996 (0.005)	0.971 (0.019)

Liver Biopsy – Stereology Services

Resonance Health can provide a quantitative assessment of hepatic steatosis of digitised biopsies using stereology. Stereology offers multiple key advantages:

- Stereology is a non-biased method that delivers a standardised assessment of steatosis from biopsies. In particular, this can add value in circumstances where more than one histopathologist is engaged across multiple study sites. As histopathological scoring for a given biopsy can vary between experts, stereology can provide a means to ascertain the extent of bias.
- Stereology can be applied retrospectively to analyse archived biopsy data originating from completed studies so as to determine if a 'drug effect' has been obscured because of disparate assessments from expert histopathologists.
- As stereology is used to determine the number of hepatocytes with fat vesicles (macrovesicular/microvesicular steatosis) within a liver biopsy, its findings are reported as a volumetric liver fat fraction (VLFF), and can be directly compared to the HepaFat-Scan measurements.

It should be noted that stereology can potentially be applied to the non-biased assessment of other disease related markers, including fibrosis, hepatocyte ballooning, and neutrophil infiltration. In view of the potential for the unbiased assessment of these clinically important biomarkers of liver disease, Resonance Health are currently pursuing methodologies to optimise this process.

Visceral, Subcutaneous, and Organ Fat in Metabolic Disease

A hallmark in the establishment of metabolic disease is the deposition of abnormal fat within and around organs and muscle tissue. In view of this, Resonance Health have developed imaging modalities that can provide quantitative assessments of visceral fat, subcutaneous fat, and epicardial fat. Such data can be used for the purposes of natural history studies, baseline assessments, and for the monitoring of drug-related effects. Given the links between hepatic steatosis, diabetes, and non-alcoholic steatohepatitis, Resonance Health have developed a number of investigational imaging tools to quantify the presence of fat within tissues such as pancreas, kidney, and skeletal muscle. These services can be scoped to meet individual requirements.

Organ Volume Measurements

Volume measurements of various organs such as liver and spleen for use in identifying disease states or tracking change over time as result of treatment.

Research Services and Collaborations

In recognising the changing needs of the clinical community and healthcare industry, Resonance Health remains committed to the development of novel, clinically relevant imaging modalities. As such, our team of scientists and academics are available to assist our pharmaceutical partners in the development of customised imaging solutions to maximise the return on their clinical trial investment.

CORE LABORATORY SERVICES

Resonance Health provides quality assured imaging analysis services and customisable project and data management services. This supports our clinical trial customers meet trial protocols and requirements stipulated by ICH-GCP and international regulatory authorities. Our project and data management services involve the provision of dedicated expert resources for trial management including the setup and management of MRI Centres, data management, reporting, and issue resolution. Pharmaceutical collaborators benefit from this full service to ensure operational excellence in the delivery and management of their studies. We strongly recommend project and data management alongside the provision of the analysis services.

Quality Assured Imaging Analysis Services

Resonance Health has extensive quality assurance processes and procedures including detailed standard operating procedures and work instructions to ensure compliance with regulatory requirements, FDA 21 CFR Part 820 and international standards certifications ISO 13485. These cover every aspect of the centralised image analysis services for clinical trials including:

- A quality control review of all image data to ensure strict adherence to the imaging protocol before analysis commences. Data is not accepted if not in full compliance and issues and resolution reported to both MRI Centre and Sponsor.
- Quantitative image analysis in accordance with SOPs.
- Second independent read of all image analysis.
- Quality Assurance checks on every result.
- Compliance with ICH-GCP and ISO certifications.
- Full audit trail.

Resonance Health has invested significant resources in the development of the HIPAA and HITECH compliant FAST system; a web-portal for the secure transmission of image data and patient results from anywhere in the world. Privacy and security of patient information is controlled via unique logon IDs and passwords. FAST has a number of stringent physical and electronic security measures and Resonance Health employs a comprehensive set of policies and procedures to ensure protected health information is secure.

Project Management Services

- Development of an Imaging charter and other study specific documentation
- Establishing study specific project management files.
- Imaging Centre selection, training, and management to ensure standardisation of imaging
- Establishing communication plans.
- Central point of contact for reporting and issue escalation.
- Reporting of trial status, such as:
    - Site and scanner setup and verification status
    - Data query trackers
    - Data reconciliation trackers
    - Subject results
    - Subject status tracker (i.e. scan due dates, completion dates, overdue scans)
    - Fully customisable reporting and cycles as requested

- Enforcing protocol patient identifier anonymity, including data query communications where necessary to confirm or correct patient identifiers.
- Trial specific standard operating procedures and detailed work instructions to ensure trial protocol requirements are met and Resonance Health staff members are trained on specific requirements.
- Dedicated internal auditing of the trial records and data management.
- Training and Qualifications: Resonance Health ensure that an adequate number of qualified personnel are assigned and trained to support all clinical trials. Training is documented and available on request if audited. Backup staff are also trained as a contingency.
- Provision of trial specific documentation as required, including an MRI Centre Manual. Protocol specific instructions can be added to the Result Reports if required (e.g. a statement added to the report depending on the liver iron concentration result indicating dosage instructions in line with the protocol guidelines). These electronic reports are designed and validated according to the client's needs.
- Compliance with all trial related regulatory requirements (in addition to ISO 13485, FDA 21 CFR Part 820 and the EU MDD), including 21 CFR Part 11, HIPAA and HITECH Acts, ICH Guidelines, EU Data Protection Directive and Safe Harbor provisions. Includes full audit trail. Induction and annual refresher for Resonance Health staff training on these requirements.
- Support Regulatory Authority (FDA) audits relating to specific pharmaceutical clinical validation trials.
- Accepting and in full support of trial vendor audit requirements, including desktop audits, conference calls and in-person inspections of the Resonance Health quality system and services.
- Full Design Control and Validation of ancillary processes and systems required for service delivery for clinical trials and record retention requirements.
- Record Retention and Storage: Maintenance of electronic and hardcopy (under lock and key) trial related records in dedicated secure locations until trial completion. As standard, all electronic and hardcopy records are retained for at least five years and in the case of clinical trials with project and data management services for at least 15 years from expiration of the agreement. Resonance Health has validated systems for storage and backup of all source data in accordance with the FDA draft guidance titled Clinical Trial Imaging Endpoints Process Standard (March 2015). All hardcopy and electronic subcontractor processes for archiving and backup are governed by a Business Associate Agreement compiled to meet ICH-GCP, HIPAA and HITECH Act requirements.

Data Management Services

- Establishment of a data transfer specification and database.
- Electronic image data tracking and management
- Blinded or un-blinded reporting of results to CRO and data cleaning as required.
- Electronic imaging tracking (using Resonance Health's secure online tracking system - FAST).