

*Imaging CROs, Clinical
Trials and Standards*

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Stakeholder perspectives

- CTO of an imaging core lab primarily involved in therapeutic oncology trials for regulatory applications
- Editor of the DICOM standard, hence biased towards standards in general and DICOM in particular
- Formerly with GE Medical Systems, hence biased towards the use of standards that add value in clinical marketplace (add commercial value to a product)
- Radiologist, hence biased towards clinical common sense, minimal impact on productivity and ease of use
- Software developer, hence biased towards ease of implementation and re-use of existing tools and components

Imaging CROs (aka. “core labs”)

love standards ... why?

Scope of Clinical Trials

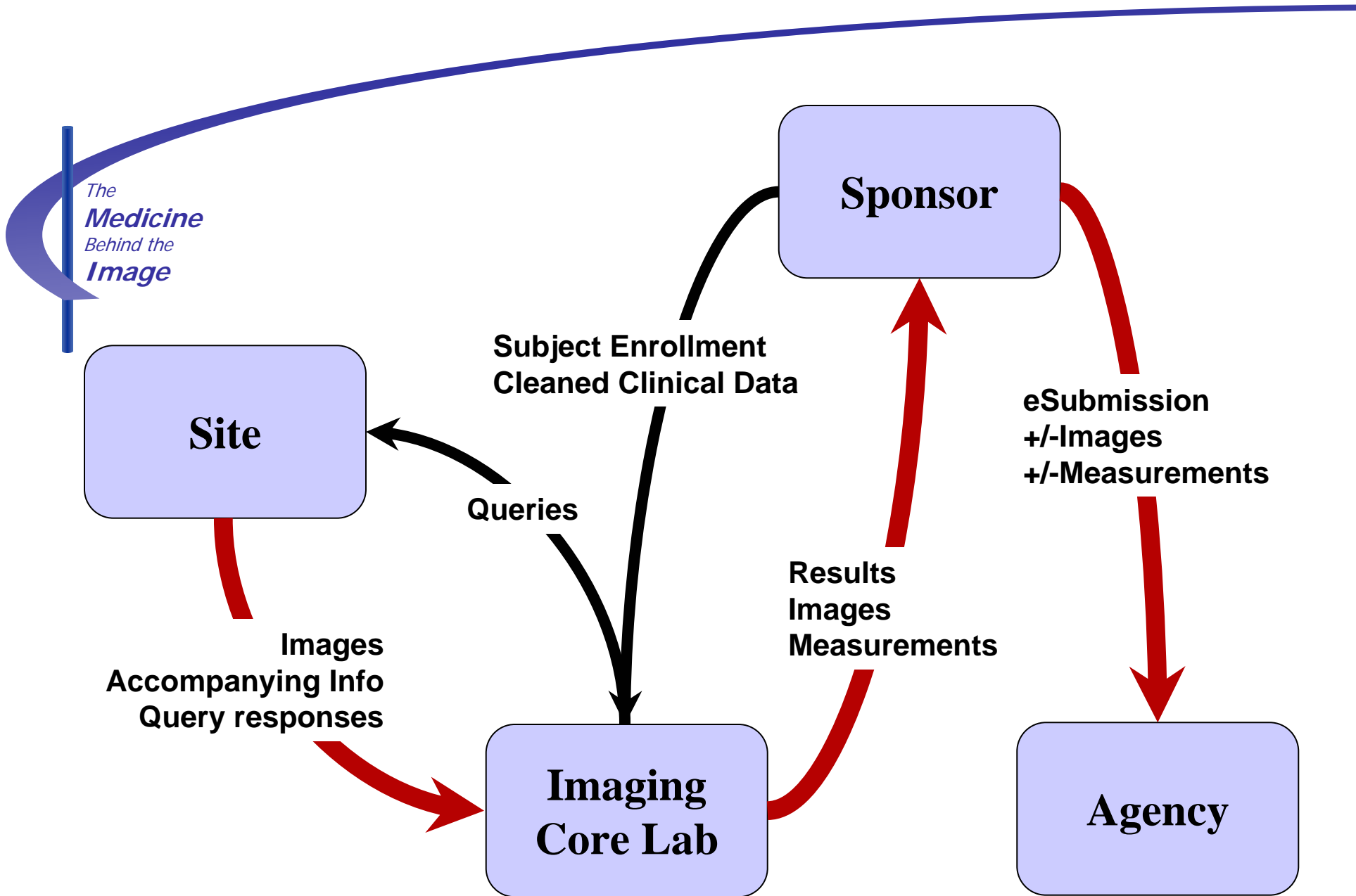
- Academic versus commercial
- Cooperative group academic trials
- Drugs versus devices
- Type of drug or biologic
- Early drug development
- For regulatory approval (Phase III)
- Imaging versus Radiotherapy

Academic v. Commercial

- Cooperative group trials
 - Typically a collaboration of universities
 - Use on-site rather than independent readers
 - Use their own infra-structure & processes
 - Not subject to regulatory oversight
 - May not need quality control, audit trails, etc.
 - No software validation requirement
- Commercial (pharmaceutical) trials
 - Recruit patients wherever they can get them
 - Outsource logistics - CROs and Imaging Core Labs
 - Independent read required (by regulatory agencies)
 - Strict regulatory oversight - vendor GCP/IT audits
 - Reduced variance and data integrity paramount
 - Strict software validation requirement

Reality Check

- A typical imaging “core lab” has ...
 - Dozens if not hundreds of trials
 - Many trials with hundreds or thousands of subjects
 - Many trials with hundreds or thousands of sites worldwide
 - Investigators are not imaging centers or radiologists



Imaging core lab functions

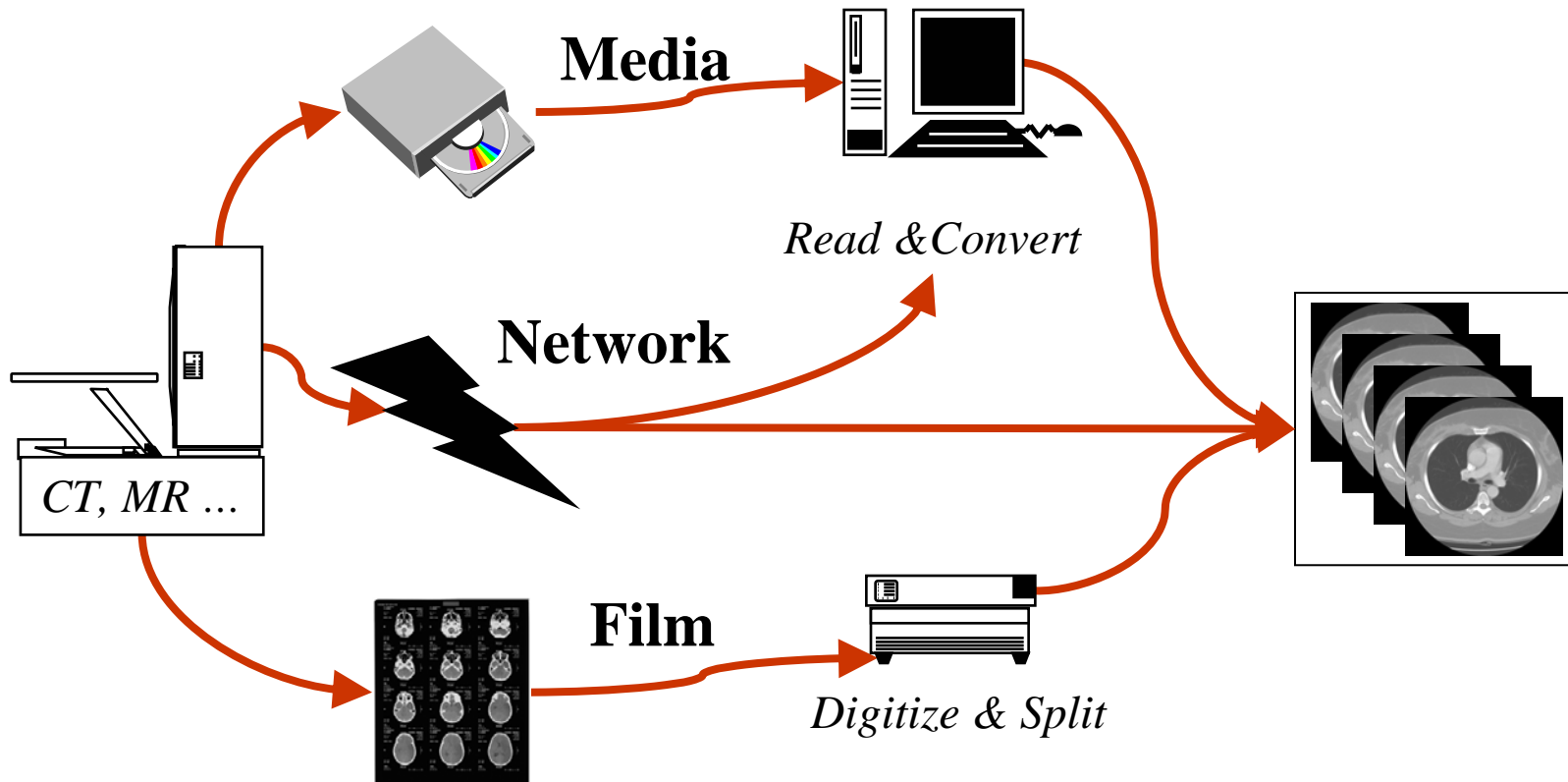
- Trial design
- Logistics of conduct of trial
- Independent review
 - quantitative & qualitative
 - human (cognitive) involvement
 - not just about change in numbers
- Submission “publishing”
- Archival

Standardization opportunities

- Trial design and conduct - UPICT (?)
- Site equipment qualification - ACR
- Acquisition of images at sites - UPICT
- Transfer of images from sites - DICOM, IHE, MIRC
- Internal use within core lab - DICOM
- Conduct of independent reads - FDA
- Response criteria and **change detection** - RECIST - future ?
- Tools for reading and analysis - ?
- Quality control, assurance and improvement - ?
- Submission to regulators - FDA ? DICOM
- Compliance and certification - e.g., no DICOM “police”
- Archival and re-use - ?
- Audit trails - IHE

The
Medicine
Behind the
Image

Image Transfer from Sites



Media Transfer Standards

- Largely a solved problem
- Standard DICOM media
 - DVD for large exams
- Standard DICOM files
- Still some obstinate PACS vendors
 - commercial priority satisfied by proprietary viewer
- Still some old equipment
 - limited number of proprietary formats
- Still some obstinate sites
 - lossy compression

Network Transfer Challenges

- Willingness
- Language barriers
- Hardware versus software in site
- Robustness of available or custom software
- IT and DICOM literacy of site
- Computer literacy of ordinary users
- Presence of modalities v. PACS in site
- De-identification issues
- Workflow issues (accompanying info & count)
- Security technology & policy (at both ends)

Future Possibilities for Transfer via Network

- Clinical need for cross-enterprise image sharing (IHE XDS-I)
- National initiatives for electronic health records
- Greater use of remote consultation
- Third party brokers, archives and repositories (such as off-site storage facilities)
- Multi-centre academic trial networks
- Federal cancer research initiatives - NCI caBIG grid tools and infra-structure
- Teaching file infra-structure (RSNA MIRC)
- Pharmaceutical trial users can leverage infra-structure
- Create a pre-competitive pharmaceutical infra-structure
- Encourage PACS vendors to support export and de-identification capabilities

De-identification Standards

- Informed consent/authorization
- HIPAA Privacy Rule 18 elements
- Common Rule, GCP and Helsinki Declaration
- Local site policies
- Sites lack good tools (commercial PACS and workstation features weak)
- Commonly used free tools damage image headers
- Removal of private elements may cause problems for advanced applications
- Identification burned in to pixel data (ultrasound, result screen captures)

IHE Clinical Trial Profile

- A patient enrolled in a multi-center clinical trial undergoes an examination, the images of which require review by a central facility.
- A technologist, nurse or physician participating in the trial uses a referring user's workstation **on the PACS** to select the relevant studies for export to the central facility.
- Replacement of identifiers and transfer to the central facility take place automatically

Standards "Inside" - Why ?

- Unequivocally, DICOM is great for receiving images from sites
- Should one use DICOM internally in an imaging core lab, for
 - Archival ?
 - Quality control and assurance ?
 - Viewing and measurement ?
 - Change detection ?
 - Submission to regulatory agencies ?

Standards "Inside" - Why ?

- Allows use of applications and tools that are
 - well-established
 - well-tested applications
 - often approved medical devices
 - subject to rigorous design controls (GMP, QSR)
- Allows choice of best-of-breed from a variety of vendors supplying to a large established market

Standards "Inside" - Why ?

- Avoids need to "reinvent the wheel" by defining one's own proprietary formats and tools
- Leverages the huge design effort invested in standards by medical device vendors and users
- Avoids the need to maintain and improve one's own internal formats and tools as technology evolves
- Leverages the clinical need for change detection and measurement, e.g., clinical mammography and lung CAD

Standards "Inside" - Why not ?

- Poorly supported in academic research software
 - new change detection and measurement tools pioneered in academic environment
 - with limited resources, focus on algorithms not robustness or ease of integration
 - may have genuine highly specific information requirements beyond the standard (e.g. functional MRI, MR spectroscopy)
 - tend to ignore information not of immediate concern (like patient identification !)
 - tend to test only with their own on-site equipment, not with a broad range of devices
 - frequently no design controls or lifecycle documentation or validation, so unacceptable for regulatory use anyway
- May be mitigated by caBIG eXtensible Imaging Platform (XIP) effort - heavily standards-based

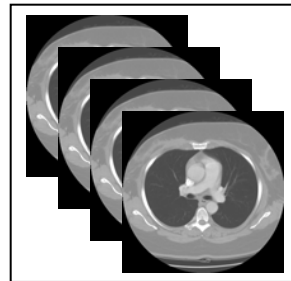
Standards for Submission

- There are no requirements for standard image format (yet)
- May need to separate images from the rest of the submission (eCTD, PDFs, SAS XPORT) due to bulk of data
- For images, DICOM makes the most sense
- For annotations and measurements on the images, there is no widely accepted standard - DICOM has Structured Reporting, but not yet widely adopted and no standard trial templates
- State of the art is to supply images + proprietary format measurements + viewing tool, either on CD, DVD or external hard drive
- If entire submission content standard, would allow agency to use their own choice of tools - currently depend on proprietary viewer per submission (training and support issues)

*The
Medicine
Behind the
Image*

Digital Image Submission

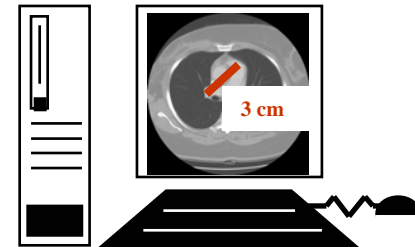
DICOM Images
DICOM Measurements
DICOMDIR



CD, DVD or External Drive

AK. 35 M
•TP1 CR
•TP2 PD
PJ. 72 F
•TP1 PR
•TP2 CR
...

DICOM Viewer



“Ordinary” PC

Standards for Audit Trails

- 21 CFR 11 requirement for records
- HIPAA requirement for access/viewing
- Leverage healthcare IT standards
 - IHE ATNA profile
 - RFC 3381- ASTM, HL7, DICOM, NEMA/COCIR/ JIRA SPC
 - Secure syslog
- Missing clinical trial profile for audit message events and content

Standards for Change Detection (in Oncology)

- WHO
- RECIST
- Volumetric measurements ?
- Functional information
 - PET SUV, DCE-MR/CT
- Why ?
 - Reduce variance to improve detection of therapeutic effect (trial size, cost)
- Why not ?
 - More sophisticated modalities - fewer sites, greater cost
 - More costly tools for analysis
 - Do fully automated tools exist or work ?
- Standards are needed *if they add value & will be used*

Conclusion

- Many standardization opportunities for core labs involved in regulatory trials
- Adoption of existing standards by sites and sponsors and core labs
- Extension of standards to specifically support clinical trial requirements
- Participation in and adoption of incipient efforts to standardize new areas (e.g., UPICT)
- Clarify role of CDISC and DIA in standards for image clinical trials
- Standards beyond RECIST for change detection need investigation
- Specific gaps that remain to be filled
- Standards may be written but not adopted
- Standards may add cost without benefit
- Compliance testing and/or certification often missing