Impact of Protocol Complexity on Digital Data Integrity Quality Assurance for Clinical Trials Requiring Digital Data Submission

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1. Abstract

Purpose: To report on impact of clinical trial protocol complexity (modality and clarity with which protocol is written) on that part of cooperative group (CG) clinical trial quality assurance (QA) review process referred to as *Digital Data Integrity QA (DDIQA)*.

Materials/Methods: Institutions participating in clinical trials utilizing 3DCRT, IMRT, SBRT, and brachytherapy must be able to submit case 3D digital datasets (planning images, contours, and dose distributions) electronically to ITC for QA review. Film/hardcopy data are not adequate for evaluating target volumes (TVs), organs at risk (OARs), and 3D dose distributions. Also, DVH data are inadequate for review without spatial information and dose fractionation information. Responsibility for QA review has been divided between ITC (*DDIQA review*) and sponsoring CG for *Protocol Compliance QA Review (PCQA)*. DDIQA checks data format, spatial registration, file corruption, and inclusion of protocol required data elements. Some structures must be renamed and non-protocol structures eliminated. ITC is developing a set of standard structure names for RTOG trials and is working to merge this set with ICRU-based volume designations. Processed data are posted to the web-based *Remote Review Tool*, a component of ITC's clinical trial QA system (QuASA2R) for CG PCQA review, which includes compliance review of TV and OAR contours as well as dose compliance review.

Results: ITC's DDIQA experience is based on receiving/processing over 7700 digital datasets over 14 years. Analysis of DDIQA metrics shows that approximately 30% of submissions are problematic and require resubmission, and that DDIQA effort expended is dependent on protocol complexity. Protocols requiring more than one fraction group have a higher incidence of problematic submissions (50% vs. 25% for all other submissions). Protocols which include contouring of nodal volumes and large number of OARs are more time consuming and require more experienced QA staff to prepare for PCQA review. IMRT submissions include non-anatomical structures used for optimization. TVs and OARs need to be combined into a single protocol compliant structure set and doses for separate fraction groups must be combined into a single total dose. Hence, H&N IMRT cases can take as long as 2 person-hours to prepare for PCQA even for non-problematic data submissions.

Conclusion: Total automation of case dataset submission for QA review is not realistic at this time. ITC's DDIQA process has proven to be an effective paradigm for facilitating protocol QA. Overall effort required for DDIQA depends on protocol complexity. Specific information included in protocols, as well as improvements in software tools can make DDIQA more efficient.

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2. Introduction

The Image Guided Therapy Quality Assurance (QA) Center (ITC) has been accepting, processing and reviewing digital data submissions for support (facilitating QA and analysis) of advanced technology protocols for more than 14 years. For the past 9 years the ITC has been a part of the NIH funded Advanced Technology QA Consortium (ATC) which consists of national QA centers. Over 7700 case data sets have been submitted and processed for review.

The ATC's QuASA²R (Quality Assurance, Submission, Archival, Analysis, and Review) system (see Panel 3) developed and maintained by the ITC, is used for all these advanced technology (AT) protocols. It provides web-based access to treatment planning data QA for all active ATC supported protocols. Protocol specific digital treatment planning data are sent to ITC via SFTP or media.

The Protocol review process pioneered by the ATC(ITC) is now clearly divided between the ITC and the cooperative groups. The ITC is responsible for **Digital Data Integrity QA (DDIQA)** which is a review for completeness of protocol required elements, format of data, spatial registration, and possible data corruption; and recalculation of all Dose Volume Histograms (DVHs). The cooperative group is responsible for **Protocol Compliance QA (PCQA)** which includes review of target volume and organ at risk contours as well as protocol dose prescription and dose heterogeneity compliance. PCQA is performed by the cooperative group designated reviewer using QuASA²R's web-based *Remote Review Tool (RRT)*. When a case is ready for review, the ITC notifies the PCQA reviewer who is responsible for the rest of the review process. This clear division of QA review process has made it more efficient for both the ITC and the cooperative group to keep track of the status of the AT protocols for QA reports and data quality reports and allows the cooperative group to request delinquent data from the participating institution in a more efficient manner.

It should be noted that the DDIQA process requires human intervention to make possible the review of a large number of the cases that are submitted to the ITC. Efficient QA tools and processes developed by the ITC have made practical the processing of large amounts of protocol data for review and analysis. Nevertheless, the receipt of reviewable digital data is often an iterative process that requires repeated correspondence with the submitting institution.

As a further step in ensuring consistency of datasets, the ITC also prepares the data for review by renaming structures, combining individual fraction groups and deleting non-anatomical/non-protocol structures so that the PI reviewer only needs to review the protocol required structures. Also, DVHs are recalculated so that a database of dose volume statistics with standard structure names exists for QA and analysis of large numbers of cases. The purpose of this report is to attempt to identify characteristics of clinical trial protocols that affect the effort required to perform DDIQA.

3. QuASA²R: Quality Assurance Submission, Archive, Analysis, and Review System

The QuASA²R system at ITC supports data collection, QA review, and outcomes analysis for cooperative-group and industrial/pharmaceutical clinical trials involving advanced-technology radiotherapy including

- Radiation Therapy Oncology Group (RTOG) [1,2]
- National Surgical Adjuvant Breast and Bowel Project (NSABP)
- New Approaches to Brain Tumor Therapy (NABTT)
- Japan Clinical Oncology Group (JCOG)
- European Organization for Research and Treatment of Cancer (EORTC).

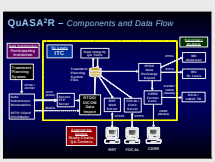

Figure 1. The QuASA²R system has been developed using a step-wise approach, since adding new capabilities must not disrupt the continuous support of ongoing protocols. [3]

- Modular architecture with emphasis on well-defined interfaces
- Integration of commercial "off-the-shelf" and open-source software
- Custom software component development focused on QA features required, but not otherwise available.

4. Data Collection and Quality Assurance for Advanced Technology Clinical Trials

The Image Guided Therapy QA Center (ITC), as part of the Advanced Technology QA Consortium (ATC), collects images and volumetric treatment planning (TP) data for Quality Assurance and outcomes analysis in advanced technology clinical trials.

Figure 2. TP datasets generally consist of the following data objects:

- Volumetric CT images
- Structure set defined by axial slice contours for target volumes and organs at risk
- Treatment plans, including beam geometry and dosimetric weighting for EBRT and source locations, strengths, (and dwell times) for brachytherapy.
- 3-D dose distributions (per fraction group) in Gy.

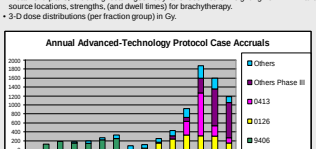

Figure 3. Over the past 14+ years, more than 7700 complete treatment planning (TP) data sets have been submitted to the ITC by institutions participating in Advanced-Technology RT Trials. The chart below shows the annual accrual of protocol cases for these studies. (Data as of September 2008.)

5. Protocol and Data Complexity Issues

The effort required to support the collection and processing of digital data for advanced technology clinical trials depends on several factors. Among these are protocol requirements related to treatment and data collection. Factors determining processing effort are enumerated below:

1. **Data submission problems** – Incomplete or inconsistent data submissions require the re-submission of datasets and subsequent re-processing of data. Panel 7 shows statistics for digital data submission problems vs. protocol disease site and treatment modality. Protocols which show the highest rate of problem submissions are those for which doses for more than one fraction group must be submitted. Institutions often send only a composite or initial fraction group, rather than one dose distribution per fraction group as required for TCP/NTCP modeling.
2. **Complexity related to dose** – For protocols requiring submission of multiple fraction groups, the ITC must sum doses prior to computing DVHs. Protocols which require high dose gradients also require the submission of high resolution dose grids. Panel 8 illustrates processing issues involving dose.
3. **Complexity related to structure delineation and naming** – Treatment modality and disease site strongly influence the effort required to perform DDIQA, as illustrated in Panel 9. H&N IMRT cases with nodal volumes are by far the most complicated handled by the ITC in terms of renaming contours and preparing data for review.
4. **Institution experience** – Institutions without prior experience in digital data submission have a higher rate of re-submission of protocol data, which decreases with experience. (See Panel 10.)
5. **Data export implementations** – As new imaging and treatment techniques are used on protocols, treatment planning data export problems become evident. Panel 11 shows examples of problems with DICOM export implementations that are discovered in the process of performing DDIQA at the ITC.

6. Digital Data Integrity QA – Data Submission Problems

Table 1. Protocol Case Digital data submissions (March 10, 2006- August 30, 2008) per protocol type and the number of problems encountered that required human intervention by ITC personnel. Note the significantly higher rate for the prostate 3D/IMRT protocol with nodal volumes. This is mostly due to the fact that this protocol requires the submission of multiple fraction groups.

Disease Site	Number of cases Digitally Submitted	Cases Requiring Human Intervention	% Cases Requiring Human Intervention
Lung	72	28	39
Prostate 3D/IMRT	1296	293	23
Prostate Seed	204	24	12
Partial Breast	1134	292	26
Liver SBRT	12	2	17
Prostate 3D/IMRT with Nodal Volumes	438	215	**49**
H&N IMRT	726	204	28
Other Pelvic IMRT	215	49	23
TOTAL	**4097**	**1107**	**27**

7. Dose-Related Complexity

In addition to experiencing a higher rate of intervention and re-submission (see Table 1) for protocols which involve submission of multiple fraction group doses, these protocols also require a greater effort by the ITC for data preparation as the individual fraction groups are combined to give a total dose. Protocols requiring high dose gradients (SBRT protocols) also complicate the submission and DVH recalculation since the resolution of the dose matrix has a noticeable effect on the time needed for DVH calculation. Below are examples of each type of complexity.

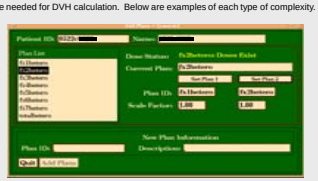

Figure 4. Tool used by ITC to combine dose files. The ITC collects individual fraction groups in order to maintain fractionation information. Each fraction group represents a set of beams that are treated for 1 or more days. The individual fraction groups are then combined to construct a dose matrix which represents the total dose delivered to a patient. This composite dose is used for the recalculation of DVHs. (Summing of individual fraction groups currently requires dose matrices with the same frame of reference, i.e. coordinate system.)

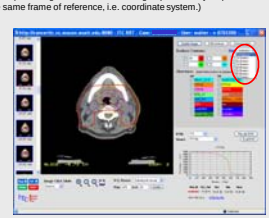

Figure 5. Example of a 3DCRT H&N case where seven fraction groups were summed to get the composite dose. Isodoses for the composite dose are shown on the figure.

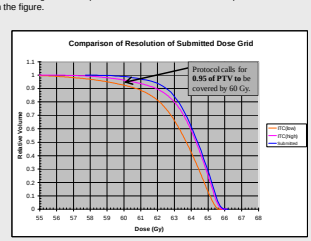

Figure 6. Comparison of submitted vs. recalculated DVHs for two different submissions to the ITC for a 5 mm dose grid (ITC(low)) and a 2 mm dose grid (ITC(high)). The dose resolution submitted has a large bearing on the calculated DVHs. The submitted DVHs are for an even higher resolution dose grid. The lower resolution DVH demonstrates a major variation according to the protocol, while the submitted DVH shows much better coverage.

8. Structure Delineation and Naming

A large source of complexity for submitted digital data is the submission and naming of structures. Protocols require certain structures for protocol compliance QA and dose volume analysis. The ITC publishes standard names for these structures, but these are not uniformly adopted in clinical practice. Simple protocols with single target volumes that do not include at-risk nodal structures are much less complex than protocols which require the inclusion of nodal volumes. Additionally, the number of OAR is significant. E.g., the anatomy for H&N is much more complex than that for prostate.

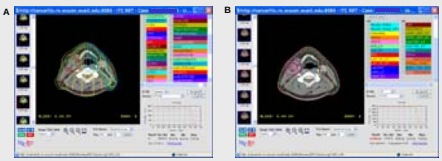

Figure 7. Images illustrating contouring of a H&N IMRT case before (A) the case is prepared by experienced ITC personnel for review and after the case is ready for review (B). Many structures used for optimization are extraneous in the review process and can be removed. Protocol-required structures are renamed to standard names. The PI physician reviewer only views the structures necessary to review protocol compliance. Before DDIQA, this case had 74 structures. After DDIQA, this case had 24 structures all of which represent anatomy and targets.

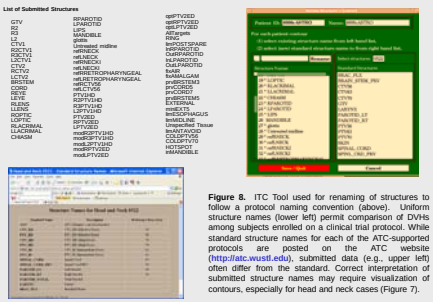

Figure 8. ITC Tool used for renaming of structures to follow a protocol naming convention (above). Uniform structure names (lower left) permit comparison of DVHs among subjects enrolled on a clinical trial protocol. While standard structure names for each of the ATC-supported protocols are posted on the ATC website (http://atc.wustl.edu), submitted data (e.g., upper left) often differ from the standard. Correct interpretation of submitted structure names may require visualization of contours, especially for head and neck cases (Figure 7).

Table 2. Handling of submitted structures for the case shown in figure 5 to prepare data for remote review by a protocol study chair. After archiving originally submitted data sets, ITC policy allows non-anatomical structures that are not required by the protocol to be discarded. One instance of each anatomical structure is always retained.

Submitted Anatomy	Disposition	Final Anatomy	Comments
GTV	No change	GTV	
R2, R3, L2	Deleted		Redundant with CTVs
CTV1, R2CTV1, R3CTV1, L2CTV1	Combined into single high dose CTV	CTV70	
Normal Structures (e.g., BRSTEM, CORD, REYE, LEYE, ROPTIC, LOPTIC, ...)	Renamed to standard names	ITC Standard Name (e.g., PAROTID_RT, PAROTID_LT, ...)	
PTV1HD, R2PTV1HD, R3PTV1HD, L2PTV1HD	CTV70 expansion, is not limited by skin.	Discarded from Review	These structures were not the final structures treated
modR2PTV1HD, modR3PTV1HD, modL2PTV1HD	CTV70 expanded and limited by skin	Combined and renamed to PTV70	
tinANTAVOID COLDPTV56 COLDPTV70 HOTSPOT	Optimization structures	Discarded from Review	These structures do not necessarily represent any anatomy and are used for optimization. Not necessary for protocol compliance review

Table 3. Dependence of the number of submitted structures on treatment modality (3DCRT vs. IMRT) and disease site. Notice that for the RTOG 0415 Prostate 3DCRT/IMRT protocol (10 required structures), the average number of submitted structures is 12 for 3DCRT cases and 14 for IMRT cases. For the RTOG 0522 H&N IMRT protocol (13 required structures), which includes more target volumes and more optimization structures, the average number of submitted structures is much greater.

Disease Site	Number of protocol structures	Number of target Volumes	# of Cases analyzed	Avg #of submitted structures
Prostate 3D	10	1 (No Nodes)	102	12
Prostate IMRT	10	1 (No Nodes	351	14
H&N IMRT	13	2-3 (includes Nodes)	491	27

9. Institutional Experience

The rate of ITC intervention and resubmission decreases as institutions learn both the complexities of each protocol and become more adept at the data submission process. The table below illustrates this learning process reflected in the decreasing rate of intervention needed over three sequential stages of participation in an advanced technology protocol.

Table 4. Resubmission/intervention rates for three stages of participation in the NSABP B39/RTOG 0413 Partial Breast Irradiation trial: (1) Dry run submissions (credentialing), (2) Rapid reviews (first case accrued by an institution using a particular treatment modality), and (3) all subsequent protocol cases. Note the trend toward improvement as institutions progress from credentialing to case submissions.

Stage of Participation	Submission Type	Cases	# Requiring Intervention	% Requiring Intervention
1	Dry Run (prior to first case)	555 (Submissions since 2006)	225	40
2	Rapid Review (first case)	329 (Entire Protocol)	109	33
3	All other Cases	1271(Entire Protocol)	305	24

10. Export Implementation Issues

As new imaging and treatment techniques are used in treatment planning for advanced technology trials, problems involving data export capabilities of TPSs may become evident. An example is the use of non-coplanar beam positions or modalities that are not yet well tested by TPS manufacturers. Two examples of problems encountered in data submitted to the ITC are shown below. The first is a case in which the scan position is not often used. The second is a recurring problem with HDR DICOM export.

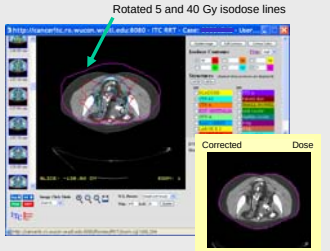

Figure 9. Submission illustrating a problematic DICOM submission due to incorrect DICOM export by the Vendor. The coordinate system defined by the DICOM files representing the CT scans and RT Structures are consistent, but the coordinate system defined by the DICOM RT Dose file is rotated 180 degrees in the axial plane. The Vendor has confirmed that the exported DICOM files were inconsistent. This was a "rapid review" requiring approval by the protocol PI before the patient could start treatment. ITC personnel were able to identify this problem during DDIQA, and to make an adjustment to the dose registration so that the case could be reviewed in the time allotted for rapid reviews (3 business days). Extensive comparisons of screen captures of isodoses provided by the institution with the corrected digital data were done to ensure the digital data correctly represented the way the patient was planned.

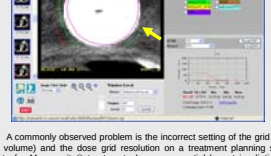

Figure 10. A commonly observed problem is the incorrect setting of the grid margin (3D calculation volume) and the dose grid resolution on a treatment planning system that submits data for Mammosite® treatment plans on a partial breast irradiation protocol. Note the breaks in the isodose lines (indicated by the arrows) and coarseness of the isodose lines in this example.

11. Discussion

The effort required to support the collection and processing of digital data for advanced technology clinical trials depends on protocol requirements related to treatment and data collection. An examination of data submission and processing statistics illustrates this dependence.

- Protocols whose targets include nodal volumes require much more effort to perform DDIQA. These cases involve interpretation of structure names and contours to determine whether all required structures are present and to prepare them for PCQA by study chairs. Use of IMRT in such studies, complicates the task further.
- A decrease in the rate of re-submission of protocol data is observed with an increase in protocol participants' experience. Protocol participants appear to benefit from feedback offered through correspondence with ITC personnel.
- New imaging and treatment planning techniques as well as updates in TP software may expose problems in the design and implementation of data export for advanced technology trials. The ITC plays an essential role in detecting and helping to correct these problems.
- The ATC facilitates the collection of complete volumetric data sets in digital format for supported cooperative groups. In addition to ensuring the quality of treatments for protocol accruals, this effort builds a rich, high-quality data base of volumetric treatment planning information that will permit data analyses beyond those defined in clinical trials protocols [1]. To ensure the quality of this database, the ITC has also facilitated the review of every submitted protocol case by a PI reviewer and consistent naming of structures.

12. Conclusions

- The processing of digital data for the review of advanced technology clinical trials requires human intervention to identify and correct errors in data submission and to prepare data for review and analysis in approximately one-fourth of cases submitted.
- The amount of effort required for DDIQA is dependent on the requirements of the protocol for which data are being collected. Protocol characteristics that influence the amount of effort required for DDIQA include the following:
  - Treatment plans involving more than one fraction group,
  - Treatment techniques producing high dose gradients,
  - Disease sites including nodal volumes (especially when treated using IMRT), and
  - Use of novel imaging techniques and treatment modalities (e.g., patient positions).
- Procedures and tools developed by the ITC have made possible the collection of a large volume of data for advanced technology clinical trials, the preparation of these data for Protocol Compliance QA, and the creation of a large archive of treatment planning data linked to outcomes for later data mining.

13. Pertinent Publications and Acknowledgements

1. Bosch WR, Straube WL, Matthews JW, Michalski JM. Deasy JO,Young B, O'Meara E, Curran WJ, Cox JD, Purdy JA, "A Survey of the ITC Volumetric Treatment Planning Data Archive Supporting RTOG Advanced Technology Clinical Trials", (Abstract) Int. J. Radiat. Oncol. Biol. Phys., 69(3), S195, 2007.
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3. Bosch W, Matthews J, Straube W, Purdy J: QuASAR: Quality Assurance Submission, Analysis, and Review System for Advanced Technology Clinical Trials in Radiation Therapy, in the Proceedings of the XVth International Conference on the Use of Computers in Radiation Therapy, June 4-7, 2007, Toronto, Canada, edited by Jean-Pierre Bissonnette, Published by Novel Digital Publishing, Oakville, Ontario, Canada, p. 98-102, 2007
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6. Sharma A, Saltz J, Pan T, Bosch W, Deasy J, Purdy J: Application of caGrid® Middleware to Facilitate Quality Assurance for Advanced Technology Radiation Therapy Clinical Trials (Abstract) In: Radiological Society of North America scientific assembly and annual meeting program. Oak Brook, Ill: Radiological Society of North America, 2007.

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