Assessment of Target Volume and Organ at Risk Contouring Variability within the Context of UK Head and Neck and Lung Cancer Radiotherapy Clinical Trials

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I, Dr John Richard Conibear, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Aims:

Radiotherapy quality assurance (RTQA) is now a requirement of radiotherapy trials since poor target volume and organ at risk (OAR) contouring has been shown to impact on patient outcomes within the context of clinical trials. The first hypothesis for this research is that statistically significant inter-observer variation exists amongst clinical oncologists' target volume and OAR contours within the context of the pre-trial quality assurance (QA) benchmark cases for four different UK radiotherapy trials. The second hypothesis is directed towards confirming that RTQA feedback during the pre-trial benchmark period does influence contouring for head and neck cancers.

Materials/Methods:

Four radiotherapy trials (ART-DECO, COSTAR, IDEAL and i-START trials) that require all prospective investigators to submit pre-accrual benchmark cases were selected. All benchmark cases until November 2012 were collected in DICOM format. The investigator contours were grouped into either target contours (TARGET) i.e. CTV1, parallel OARs (OAR-P) i.e. parotid glands, lungs and heart or serial OARs (OAR-S) i.e. brainstem, spinal cord and oesophagus. These were then analysed using a tumour management group (TMG) consensus contour to determine whether statistically significant differences existed between them. The local conformity index (L-CI) for each structure was also calculated for analysis.

Results:

Analysis of the pre-trial benchmark cases revealed statistically significant differences ($p=<0.05$) between clinical oncologists' target volume, serial and parallel OAR contours. Analysis of the resubmitted head and neck pre-trial benchmark cases also revealed statistically significant differences between first and subsequent submission contours.

Conclusions:

This research revealed that a statistically significant difference does exist in clinical oncologists' target volume and OAR contours within the pre-trial QA benchmark cases for both lung and head and neck cancers. It was also revealed that RTQA feedback during the pre-trial benchmark period had a positive and statistically significant impact on head and neck clinician contouring.

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Chapter 1: Introduction

The terms accuracy and precision are used in the context of measurement. Accuracy refers to the degree of conformity and correctness of something when compared to a true or absolute value. Precision on the other hand describes the variation you see when you measure the same part repeatedly using the same device.

Observer variation is the failure of an observer to measure or identify a phenomenon precisely which in turn results in an error. Two types of observer variation exist, inter and intra; inter-observer variation is the difference that exists between different individuals assessing the same information and intra-observer variation is the difference that exists when one individual assesses the same information but on more than one occasion.

Both types of observer variation exist in all aspects of medicine. Clinical oncology as a sub-specialty is not immune from observer variation as it relies upon a clinician's own interpretation of clinical and radiological data when making treatment decisions. Sources of error in clinical oncology can include the observer missing an abnormality i.e. incorrectly identifying the true extent of a patient's tumour, the use of erroneous techniques or imprecise tools resulting in incorrect measurements, or simply the misinterpretation of the data itself i.e. misinterpreting normal tissues as being abnormal.

One of the principle tasks clinical oncologists perform in the era of 3D conformal radiotherapy is the delineation of the patient's tumour, termed the target volume, and the delineation of normal organs around the tumour, which are termed the organs at risk (OAR). Clinicians delineate these structures on computers using radiotherapy treatment planning software. This task is potentially prone to both inter and intra-observer variability depending upon the clinical circumstances [1].

The first hypothesis of this research is to confirm whether a statistically significant difference in inter-observer variation also exists between oncologist's target

volume and OAR contouring within the clinical trial benchmarking period for lung and head and neck cancers. This hypothesis will be tested by quantifying inter-observer variation amongst participating UK head and neck and lung cancer clinical oncologists by analysing their pre-trial benchmark QA target volume and OAR contours. It also aims to demonstrate that RTQA feedback during the pre-trial benchmark period helps to reduce inter-observer variation in target volume and organ at risk contours by analysing resubmission benchmark data.

This research will not assess intra-observer variation as strictly speaking the re-submissions were not true intra-observer re-assessments but were driven instead by specific advice and feedback from the respective trials RTQA teams.

Recent Advances in Radiotherapy

Over the last 50 years' external beam radiotherapy (EBRT) has undergone refinement through the discovery of X-ray computed tomography (CT) and advances in linear accelerator design. Up until the early 1990s curative external beam radiotherapy for cancer patents was typically planned and delivered using a 2-dimensional technique usually termed 'conventional radiotherapy'. This technique meant that the patient's underlying cancer and a significant proportion of their surrounding normal tissue was encompassed within a typically box shaped radiation field. Due to the uncertainties of tumour location and organ movement, shielding of normal tissue was relatively minimal. This of course meant that the volume of normal tissue treated was great and that patients often developed significant acute toxicities [2]. Because of these toxicities patients were often unable to tolerate radiotherapy doses more than 67-70Gy when delivered using conventional radiotherapy.

The discovery of CT imaging and its integration into radiotherapy planning during the 1980s led to the creation of 3D conformal radiotherapy (3D-CRT) [3]. This term describes how the linear accelerator performs complex beam shaping to conform the X-rays to match the outline of the patient's tumour on the patient's treatment-planning scan. Conforming the beams also helps to minimise the dose of radiation delivered to the patient's normal organs.

Initial studies comparing conventional radiotherapy to 3D-CRT found that 3D-CRT helped reduce toxicity whilst maintaining disease control. One phase III randomised controlled trial comparing 3D-CRT with conventional radiotherapy using a standard dose of 64Gy to treat prostate cancer showed a significant reduction in the dose limiting late side effect of proctitis with no impact on disease control when using 3D-CRT [4].

More recent advances in 3D treatment planning software and computer-controlled linear accelerators has led to the creation of a high precision form of 3D-CRT termed 'intensity modulated radiotherapy' (IMRT). Using IMRT, physicists can deliver precise radiation doses to a tumour whilst minimising the dose to surrounding normal tissues by planning more complex treatments utilising an increased number of X-ray beams, sometimes as many as 9. IMRT planning permits an even higher level of dose conformity to be achieved.

The adoption of IMRT and inverse planning techniques has allowed clinicians to increase the dose delivered to the patient's cancer whilst maintaining acceptably low doses of radiation to the patient's normal intracranial, intrathoracic, abdominal or pelvic organs. The advent of 3D-CRT, and now more recently IMRT, has helped to reduce the incidence of both the acute and late toxicity commonly associated with radical radiotherapy. These new radiotherapy treatment techniques have also permitted the exploration of dose escalation in the radical treatment of many different tumour sub-types.

The Role of the Modern Clinical Oncologist

Over the past century, the role of the clinical oncologist has also evolved as a direct result of the advances made in radiotherapy planning and delivery. The transition from 2D conventional to 3D-CRT planning saw radical changes about the clinical oncologist's role in target volume delineation. Clinicians who bridged this transition had to adapt and learn entirely new skills and concepts to be able to fully embrace the 3D-CRT era.

To help facilitate the transition from conventional 2D to 3D-CRT the International Commission on Radiation Units and Measurements (ICRU) published several key reports which would define the fundamental concepts of 3D-CRT planning and reporting. The reports would be used as benchmarks to standardise the terminology and rules used throughout the world to define 3D-CRT [5-7]. By using the published ICRU reports as a framework, clinicians could adopt a unified approach to 3D-CRT planning and reporting.

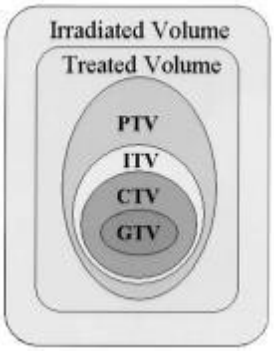


Figure 1: ICRU 50 / 62 Volume Definitions [8]

Now because of this evolution, clinical oncologists are tasked with delineating 3D target volumes based upon their patient's own CT planning data. Using the target volumes defined in ICRU 50 and 62 clinicians are expected to outline the patient's 'gross tumour volume' (GTV). The GTV is the primary tumour or other tumour mass shown by clinical examination, at examination under anaesthetic (EUA) or by imaging. The GTV is classified by tumour staging systems such as TNM (UICC), AJCC or FIGO. The tumour's size, site and shape may appear to change depending on the imaging technique used and an optimal imaging method for each tumour site must therefore be specified. The GTV may encompass the primary tumour and/or involved lymphadenopathy and/or distant metastases. The GTV always contains the highest tumour cell density and is absent after complete surgical resection [9].

Any areas considered at risk of subclinical invasion are termed the 'clinical target volume' (CTV) and will normally encompass the GTV when one is still present (see Figure 1 above). The definition of the CTV is based on the histological analysis of post-surgical and post mortem tumour specimens. These specimens were analysed to determine the extent of tumour cell spread around the gross GTV as described by Holland et al. [10]. The GTV-CTV margin is also derived from the biological characteristics of the tumour, patterns of local tumour recurrence and the experience of the treating oncologist. Manual editing of the CTV margin is therefore allowed to account for these factors and anatomical barriers to tumour spread. An appropriate margin is then added to the CTV to create a 'planning target volume' (PTV). The PTV margin accounts for intra and inter-fractional changes in tumour size, location, variations in patient positioning and changes in alignment of the treatment beams (setup margin).

Any normal organs within or near to the treatment area should receive as low a dose of radiation as possible [6, 7]. These normal organs are termed the 'organs at risk' (OAR) and change depending upon the site within the patient's body that is being irradiated. The ICRU report described OARs as having distinct tissue architectures; serial OARs, for example, the spinal cord, have a high relative seriality implying that dose above a tolerance limit, even to a small volume, impairs the function of the entire OAR; parallel OARs, for example, the lungs, have a low relative seriality where the main parameter impairing the organ's function is the proportion of the OAR receiving a dose above a specified tolerance. In reality though, many organs have tissue architecture with both high and low seriality components.

This modern, individualised, three or four-dimensional approach to radiotherapy planning now depends heavily on the clinician's own interpretation of radiological cross-sectional anatomy and requires clinicians to differentiate between 'normal' and 'abnormal' body tissues. This of course makes the process of target volume delineation highly observer dependent and at significant risk of inter and intra-observer variation.

Variation in CTV delineation by the clinician is the greatest geometric uncertainty in the whole treatment process. Studies conducted comparing the outlines of radiologists with clinical oncologists have shown significant inter-observer variability for both the GTV and/or CTV for multiple different tumour sub-sites. The magnitude of this inter-observer variability has also shown to be greater than any intra-observer variation [9]. Improvements can be made through training in cross-sectional anatomy which enables clinicians to distinguish normal structures more clearly e.g. blood vessels from lymph nodes, and to identify the extent of structures more accurately on cross sectional imaging i.e. the oesophagus on CT or MRI. Joint outlining by an oncologist and a radiologist can also help improve consistency and the use of consensus guidelines such as the head and neck nodal atlas by Gregoire et al. or the pelvic nodal atlas by Taylor et al. can improve the reproducibility of CTV delineation significantly [11, 12].

Ensuring Quality and Safety in Modern Radiotherapy Delivery

Modern radiotherapy bears little resemblance to its early form despite relying upon the same fundamental scientific principles. Twenty first century practitioners of radiation therapy can now use CT plus the possibility of other diagnostic imaging technologies to delineate a 3D target which is representative of the patient's cancer whilst observing its relation to the normal tissues surrounding it. With the ability now to also integrate real time imaging into the radiotherapy treatment process it is now also possible to track the tumour within the patient body to ensure the target is not 'missed' during the radiation treatment if it moves.

Consequently, radiotherapy departments now rely upon advanced computer technology and highly skilled clinical and non-clinical staff to target and deliver radiotherapy treatments. These technological advances though have led to increasingly complex processes which in themselves increase the risk of human and technological errors. To ensure patients are treated safely and accurately new systems and checks have had to be designed to minimise these risks; both technological and human. At every point now in the patient's treatment pathway

checks are in place to help minimise error to ensure that patients receive the highest quality of care.

UK hospitals are governed by strict legislation which outlines the safe implementation and utilisation of radiation; the Ionising Radiation Regulations 1999 (IRR 1999) and the Ionising Regulations (Medical Exposure) Regulations 2000 (IRMER 2000) [13-15]. These regulations define how radiation in the context of medicine should be safely managed to ensure patients, public and staff are not exposed to radiation unnecessarily. These regulations form the cornerstone of radiation protection within UK hospitals. With the ongoing advancement in radiotherapy treatment technology and delivery techniques clear guidance is needed to ensure clarity within radiotherapy departments internationally. This is achieved through regular publications from the International Commission on Radiation Units and Measurements (ICRU). Their publications on measurements, prescribing, recording and reporting of photon beam therapy ensures unity of standards internationally [6, 7, 16, 17].

Nationally bodies such as the Royal College of Radiologists (RCR) also play an important role in improving modern radiotherapy standards. They have published guidance on a variety of important topics aimed at improving UK radiotherapy standards; for instance, their publication 'On Target: Ensuring Geometric Accuracy in Radiotherapy' which explains the significance of systematic and random errors typically associated with 3D-CRT radiotherapy. This particular publication provides clear guidance on what can be done to minimise errors and improve the accuracy and reproducibility of modern radiotherapy delivery [18]. A combination of international guidance, national government regulations, published guidance from important bodies and the skilled training of hospital staff that provides the basis for modern radiotherapy services in the UK.

Target Volume Delineation Accuracy and Inter-Observer Variation

With the advent of 3D-CRT and its evolution to IMRT, modern radiotherapy now allows us to achieve optimal dose coverage of treatment target volumes. Consequently, it is of critical importance that target volumes are delineated

accurately to ensure adequate dose coverage whilst minimising dose to normal surrounding tissues. Even prior to 3D-CRT, inter-observer variation had been found to exist in 2D conventional planning [19].

Grabarz et al. conducted a study to describe the degree of inter and intra-observer variability in target and field definition when using 3D volume vs. 2D field-based planning. The study utilised 9 palliative cases (3 bone metastases, 3 palliative lung cases and 3 abdominal pelvis soft-tissue masses) which were given to 5 radiation oncologists participating within the study. The radiation oncologists were asked to create two sets of treatment fields, one using a 2D field-based approach and the second using a 3D volume-based approach. Once created, the 2D and 3D volumes were analysed for inter and intra-observer variations in target definition by determining the percentage overlap, under-coverage and over-coverage. The study found that the degree of inter-observer variation for 2D and 3D planning was similar with a degree of overlap of 76% (range 56% - 85%) and 74% (range 55% - 88%) respectively. Comparison of the 2D and 3D treatment fields defined by the same clinicians revealed a mean degree of overlap of 78%; over-coverage was 22% and under-coverage, 41%. Statistically there was significantly more under-coverage when field-based planning was used for bone metastases (33%) compared with the other anatomical sites studied. The author, based on their findings, concluded that 2D planning is more likely to result in geographic misses in bone metastases compared with other areas and that clinically significant inter and intra-observer variation exists in palliative radiotherapy planning [19].

Due to the increased complexity of 3D conformal target volume delineation it comes as no surprise that studies examining inter-observer variation during the 3D outlining process have found significant inter-observer variation in target volume outlines [19-28].

Wachter et al. examined the benefits of integrating axial and sagittal MRI into prostate contouring on CT with the aim of improving localisation of the prostatic apex through an inter-observer analysis. The study found that the apex of the prostate could be discriminated more easily using the MRI rather than the CT with

best judgement seen using the sagittal MRI sequences. The inter-observer variation for the definition of the prostate apex was smaller and statistically significant (p=0.009) for the sagittal MRI compared to the axial MRI and CT. They concluded that the addition of MRI provides superior anatomical information for the purposes of target outlining and thereby helps to avoid the unnecessary irradiation of healthy tissues [20]. A similar study by Cattaneo et al. looked at target delineation in post-operative radiotherapy of brain gliomas and the impact image registration of pre-operative MR on treatment planning CT scans had on inter-observer variability. They also concluded that the use of CT and MR registered imaging reduced inter-observer variability in target volume delineation for post-operative irradiation of high grade gliomas and that smaller margins around target volume could be adopted in defining irradiation technique [23].

A study conducted by Wu et al. looked at inter-observer variation in cervical cancer tumour delineation for image-based radiotherapy planning among and within different specialties and found that despite the improvements MRI imaging could bring to the resolution and definition of anatomical structures there was still "human" variations which could overshadow the gains made from these technological advancements [21]. The challenges noted for tumour delineation in this study included partial voluming by parametrial fat at the periphery of the uterus; (2) extension of the tumour into parametrial space; (3) similar signal intensity of structures proximal to the tumour such as ovaries, muscles, bladder wall, bowel loops, and pubic symphysis; (4) post-radiation changes such as heterogeneity and necrosis; (5) susceptibility artefacts from bowels and vaginal tampons; (6) presence of other pathologies such as atypical myoma; (7) factors that affect pelvic anatomy, including the degree of bladder distension, bowel interposition, uterine malposition and retroversion [21]. The conclusion of the author, based on their study findings, was that strategies needed to be developed for standardization and training in tumour delineation [21].

A systematic review conducted by Loo et al. evaluating inter-observer variation in parotid gland delineation and its impact on intensity-modulated radiotherapy solutions also found that significant inter-observer variation exists in parotid gland

delineation in the context of head and neck radiotherapy planning [22]. Their study found that almost half of the contours (46%) produced by the participating radiation oncologists and radiologists were sufficiently different enough from the contour used clinically to have necessitated a different IMRT plan if used. This study helps to highlight the impact normal organ outlining can have on radiotherapy planning and the study team concluded that strategies, such as consistent guidelines, were needed to improve inter-observer consistency in parotid gland delineation [22].

A study by Lorenzen et al. has specifically looked at the impact of guidelines on the degree of inter-observer variation in the delineation of the heart and left anterior descending coronary artery (LADCA) in the context of breast radiotherapy planning [24]. Their study found that common guidelines for the delineation of the heart and LADCA helped reduce spatial variation in the heart and length of LAD contoured which helped to reduce inter-observer variation and consequently the mean and maximum estimated radiotherapy doses to the heart [24].

Therefore to help improve both target volume and normal organ delineation accuracy and thereby reduce inter-observer variation a number of successful strategies have been examined including the use of contrast [29, 30], the use of fiducial markers [31], the addition of complimentary imaging modalities such as FDG-PET [32] and MRI [33], the aid of a dedicated diagnostic radiologist during target volume delineation [30, 34] and the use of protocols which define precisely how structures should be accurately delineated [35-37]. These studies have revealed that that implementing such strategies can improve target volume accuracy and reduce inter-observer variation. Failure though to incorporate such strategies has also been shown to impact negatively on patient outcomes and none more so than trial protocol compliance.

The Trans-Tasman Radiation Oncology Group (TROG) 02.02 trial HeadSTART was a phase III head and neck chemoradiation study evaluating the potential benefits of a new oral radiosensitiser called tirapazamine [38]. The trial was designed to detect a 10% improvement in overall survival (OS) at 2 years attributable to the

tirapazamine. Patients with squamous cell carcinoma of the head and neck were randomised to either tirapazamine, cisplatin and radiotherapy or cisplatin and radiotherapy alone. The radiotherapy in both arms was to be delivered using standard treatment fields and IMRT was not permitted.

The trial was designed so that once a patient's radiotherapy planning had been completed it was to be submitted to the Quality Assurance Review Centre (QARC) for interventional review before the end of the first week of the patient's radiotherapy treatment. The QARC would then provide feedback to the submitting centre on whether the plan was compliant with the trial protocol. If not the QARC would advise on appropriate modifications to the plan to make it compliant and then for the plan to be re-submitted. This system of radiotherapy quality assurance (QA) was a semi-prospective one to ensure protocol compliance early in the patient's treatment. Once the patient had completed their radiotherapy treatment all the patient's radiotherapy data was re-submitted for further retrospective review by the tumour management group (TMG).

By the end of the trial, a total of 853 patients had been enrolled and 820 plans were available for retrospective review (33 plans were non-evaluable). Of these 74.6% (612) were deemed protocol compliant and the remaining 25.4% were judged non-compliant (208). Of the 208 non-compliant plans, the TMG then assessed whether the non-compliance would have any adverse impact on treatment outcome. They determined that 53% (111) of the non-compliant plans would have no likely impact on treatment outcome but that the remaining 97 plans would have a major adverse impact. Of the 97 non-compliant plans 24.7% (24) had incorrect target volume definitions, 42% (41) had inadequate tumour dose coverage, 25.8% (25) had incorrect dose prescription and 7.2% (7) had excessively prolonged treatment schedules. Despite the trial being designed to detect an OS benefit because of the addition of tirapazamine, due to the poor radiotherapy protocol compliance there was a 20% reduction in OS regardless of randomisation arm.

The TROG 02.02 trial highlights the importance of protocol compliance and the potentially damaging effects poor outlining, poor radiotherapy planning and basic

errors in dose prescriptions can have on patient survival. Unfortunately, the TROG 02.02 trial is not the only one to highlight these problems. More recently Abrams et al. showed that in the Radiation Oncology Group (RTOG) 9704 study which looked at the potential benefits of chemotherapy and chemoradiotherapy in patients who had had resected pancreatic tumours, that deviation from the radiotherapy trial protocol resulted in inferior survival in patients [39].

Further studies have also revealed that protocol deviations resulting in poor target volume delineation can result in increased acute radiation toxicity. On retrospective review of the RTOG 0411 trial data it was found that > grade 3 gastro-intestinal toxicity was significantly increased in patients who had been treated with major deviations from the trial protocol (45% vs. 18%). A breakdown of the major deviations revealed that many clinicians were unable to delineate the GTV accurately with some GTV's being >5cm larger than the actual tumour size seen on diagnostic imaging [40]. Such findings highlight the importance of accurate target volume delineation both in terms of minimising toxicity and maximising treatment outcomes.

The Importance of RTQA and its Role in UK Radiotherapy Trials

To help ensure cancer patients are treated to the highest standards the ability to assess quality of care has become a national priority because deviations from accepted standards of care can lead to disparities in the quality of care delivered to patients.

National and International bodies have been tasked with the creation of best practise guidelines as well as quality indicators which can be used to monitor the quality of radiotherapy practise being delivered e.g. the UK's National Radiotherapy Dataset (RTDS). These radiotherapy quality assurance indicators can also be used to help guide the implementation of new radiotherapy techniques into routine clinical practice.

In terms of radiotherapy clinical trials, deviations from accepted standards of care can also have direct and important implications on clinical trial outcomes and can potentially confound the question the study has been designed to address.

A lack of integrated radiotherapy quality assurance within a clinical trial can also lead to scepticism surround the trials findings as was demonstrated in the European Study Group for Pancreatic Cancer 1 Trial (ESPAC-1 trial) where a lack of robust radiotherapy quality control was the focus of much criticism following the publication of its results [41]. The ESPAC-1 trial was a phase III, randomised trial of adjuvant chemotherapy or chemoradiotherapy for patients who had had pancreatic cancers resected.

The trial reported that adjuvant chemoradiotherapy for resected patients had a deleterious effect on overall survival [42]. However, due to criticism of the trials radiotherapy quality assurance and the uncertainty this may have had on the validity of the trials findings with respect to chemoradiotherapy, the United States National Comprehensive Cancer Network (NCCN) guidelines have not been altered to omit recommendations for adjuvant chemoradiotherapy for patients with resected pancreatic adenocarcinoma [43]. The ESPAC-1 trial highlights the importance radiotherapy quality assurance (RTQA) can have on radiotherapy trial outcomes as without it, perceived flaws in radiotherapy quality can hold back major practise changes despite statistically significant trial findings.

A meta-analysis of eight cooperative group radiotherapy clinical trials by Ohri et al. and a literature review of seventeen multicentre trials by Fairchild et al. have also demonstrated that radiotherapy protocol deviations can have a deleterious effect on clinical trial outcomes [44, 45]. As Ohri et. al concludes based on the findings of their meta-analysis of four paediatric and four adult multi-institutional radiotherapy trials, radiotherapy protocol deviations are associated with increased risks of treatment failure and overall mortality [44].

Now with a growing weight of international evidence showing the negative consequences poor radiotherapy protocol compliance can have on patient outcomes it has now become almost mandatory for radiotherapy trials to include a

comprehensive package of quality assurance [44-46]. As already mentioned, the TROG 02.02 study and others have highlighted the critical impact of protocol compliance on the treatment of advanced head and neck cancers. The TROG 02.02 study showed that major deficiencies in radiotherapy treatment plans resulted in a 20% decrease in overall survival regardless of randomisation arm [38].

In the United Kingdom (UK) the National Cancer Research Institute (NCRI) Radiotherapy Trials Quality Assurance (RTTQA) Group has been tasked with ensuring that all participants in NCRI badged trials adhere to the relevant trial protocol [47]. The RTTQA group achieves this through a program of activities tailored towards the clinical trials objectives. Since its inception, the RTTQA group has developed its program of QA activities to account for new techniques and advances in planning and delivery systems. When first established the focus of trial QA was predominantly treatment machine focused but over the past decade this has developed to include all aspects of radiotherapy delivery from target volume delineation to IMRT verification. Before a centre can participate in a UK NCRI trial they are required to complete all steps of the trial specific RTTQA accreditation process. This accreditation process now typically includes pre-trial benchmark outlining cases which have been designed to ensure clinicians are following the guidance set out in the trial protocol.

The addition of pre-trial benchmark cases to the activities performed by the RTTQA group has meant that new systems have had to be developed to robustly assess participating trial centres prior to trial patient recruitment. These robust systems have been designed to ensure participating clinicians meet the minimum standards of target volume delineation for that trial. To this end, the pre-trial benchmark cases are focused upon ensuring clinicians can achieve a minimum standard and consequently all modern NCRI trials have adopted this strategy.

In the UK, all NCRI trial pre-trial benchmark cases are available for download from the RTTQA's website. All centres wishing to participate in a trial are expected to download and complete them before they are permitted to recruit patients into the trial. Once a centre has submitted their completed cases for review they are

assessed by the trials own QA team which typically comprises of one or more expert clinicians from the trials TMG plus one or more members of the RTTQA group who have been assigned to oversee the QA specific activities of the trial. The duties of the QA team include ensuring that the submitting clinician has followed the instruction contained within the outlining protocol to construct their target volumes and normal tissue structures. If after review by the QA team it is felt that improvements could be made, then constructive feedback is produced by the QA team and sent back to the trial centre to help them re-evaluate their contours prior to them re-submitting them. This process is normally repeated until it is felt by the central QA team that the centre has met the minimum QA requirements of the trial.

Measuring Target Volume and Normal Tissue Inter-Observer Variability

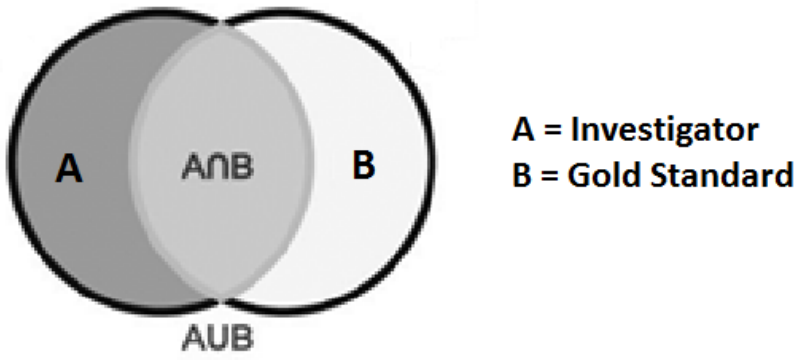
In the past, most UK pre-trial outlining benchmark case assessments were performed by direct visual inspection of all submitted contours by the central QA team. More recently a system of pre-trial benchmark quality assurance utilising a '*gold standard*' contour set has been adopted. This method relies upon the creation of reference set of contours termed the '*gold standard*'. These '*gold standard*' reference contours can be created in either one of two ways; either by an expert individual or through the consensus agreement of a panel of expert clinicians [48-53]. This latter technique now seems to be the more common method of defining the reference or '*gold standard*' contours although the former method continues. The benefit of having a pre-defined set of reference contours is that all submitted pre-trial benchmark contours can now be quickly and easily compared against the reference set either visually or using more advanced computer software which can measure different conformity indices.

Conformity indices (CIs) are numerical metrics calculated using mathematical formulae which define concordance based on variations in volume and spatial relationships [54]. Simply put they are a measurement of the common volume included in 2 volumes or a comparison of a common or consensus volume of several volumes with each of the constituent volumes [27].

A systematic review looking at the geometrical analysis of radiotherapy target volume delineation conducted by Hanna et al. in 2010 found a total of 63 published studies which used either simple volume metrics or CIs to compare target volumes. The review found that the majority of published studies (84%) relied upon simple volume measurements when comparing target structures and only 30% of the studies utilised CIs when comparing radiotherapy volumes [55].

The problem with simple volume measurements is that unlike CIs they do not give you any information on the spatial relationship between two volumes i.e. the common volume included in both radiotherapy volumes. The spatial relationship between two volumes; where A is, the investigator outline and B is the gold standard outline, can be analysed in several different ways depending upon the CI used.

The most common CI metric used in volume analysis is the concordance index which is also known as the Jaccard similarity coefficient or Jaccard conformity index (JCI) [55-57]. The JCI is the ratio of intersection of two volumes, as compared with the union of the two volumes under comparison:



$$\text{JCI (Concordance Index)} = \frac{A \cap B}{A \cup B}$$

The Jaccard Index can be reported as a fraction or as a percentage if multiplied by 100 [55]. Other commonly used CIs are the Dice Coefficient (DC) [55], van't Riet

Index [58], Discordance Index (DI) [59] and Geographical Miss Index (GMI) [60]. The DC and Van't Riet indices assess for variations in under and over outlining.

$$\text{Dice Coefficient (DC)} = \frac{2(A \cap B)}{A + B}$$

$$\text{Van 't Riet Index} = \frac{A \cap B}{A} \times \frac{A \cap B}{B}$$

The DI is useful in assessing over outlining and conversely the GMI is useful in determining the extent of under outlining:

$$\text{For 'over outlining' you can use the Discordance Index (DI)} = \frac{1-(A \cap B)}{A}$$

$$\text{For 'under outlining' you can use the Geographical Miss Index (GMI)} = \frac{B-(A \cap B)}{B}$$

Evaluation of Parameters for Quantifying Inter-Observer Variability in Target Volume Definition

Currently there are a large selection of parameters which can we used to evaluate inter-observer variability within the context of radiotherapy clinical trials. These parameters can be classified into three main group according to their methodology [61].

The first group contains descriptive parameters which describe the distribution of volumes, such as average or mean (if normally distributed), median or mode (if non-normally distributed), standard deviation, standard error, range of volumes or maximum or minimum volumes [62], ratio of the largest volume to the smallest and

dispersion of the distribution i.e. coefficient of variation (COW). These simple volume assessments are easy to measure, and relatively free from interpretation bias. Simple volume parameters also have the advantage of producing continuous variables that are amenable to statistical analysis and parametric and non-parametric calculations [55].

The second group contains parameters which deal with measures that describe the area of overlap between contoured volumes and includes the Jaccard index, discordance index (DI), geographical miss index (GMI), Dice coefficient and Van't Riet Index. Due to the large number of available metrics, this second group of parameters is the one where harmonisation in reporting is lacking [61]. It is also the group of parameters which reported studies seem use to quantify inter-observer variability in target delineation most often [62-73]. Parameters within this group can also be selected to assess specific variances between contoured volumes such as under (GMI) or over outlining (DI). The advantage of the parameters in this group is that they provide a single measurement of volumetric and positional change but are therefore prone to missing subtle areas of variation within a volume and have been shown to correlate poorly with length.

The second group also contains parameters which can be used to assess 3D structures and the volume of displacement in space i.e. variation of the centre of mass (COM). Such parameters rely upon the reconstruction of surface points on the base of meshes and then utilise 3D vectors to represent the differences on the surfaces of structures which permits the exact topographical identification and visualisation of disagreements [67, 69, 74-79]. A centre of mass analysis is useful for describing displacements or differences in locations of volumes but is unhelpful for the comparison of volume size. It is theoretically possible that two volumes under comparison could have the same centre of mass but different simple volume measurements (see Figure 2 below).

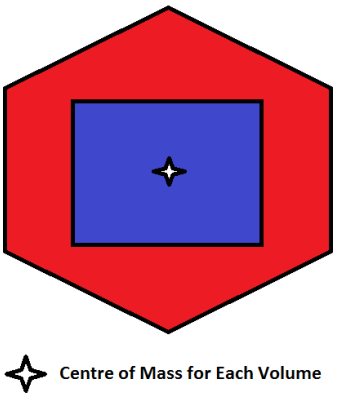


Figure 2: Two Volumes with Different Sizes but The Same Centre of Mass

The third group contains parameters which utilise statistical measures of agreement such as intraclass correlation coefficients (ICC), κ statistics (Fleiss or Cohen) or other reliability analysis tools [29, 52, 63, 67, 73, 80-82]. The κ statistics can be utilised to measure the magnitude of agreement between either two outlines (Cohen Kappa) or multiple outlines (Fleiss' Kappa). The measure calculates the degree of agreement in classification over that which would be expected by chance. Fleiss' kappa can be used only with binary or nominal-scale ratings and Cohen's kappa coefficient is a statistic which measures inter-rater agreement for qualitative (categorical) items. For both Fleiss and Cohen Kappa statistics, there is no information on the direction of the error and both require a decision made on what level of agreement is acceptable. Table 1 below summarises the commonest used parameters from each group.

Based on published reviews of different comparison methods used to assess radiotherapy target volume delineation there does not seem to be a perfect parameter which fully characterises geometrical volume differences, positional changes and inter-observer variability [55, 61]. Instead, each comparison method seems to offer distinct advantages and disadvantages and should be selected based upon the focus of the research. Hanna et al. recommends combining a simple volume parameter with a parameter that measures positional displacement, such as the centre of mass or the concordance index [55] whilst Fotina et al. recommend adding a further statistical measure of agreement to permit full reporting of the variability in delineation.

Conformity Indice Name	Description of Metric	Advantages	Disadvantages
Jaccard Conformity Index (JCI) **Van't Riet** **Dice Coefficient**	• Ratio of the volume of overlap of two structures over union volume of the 2 structures	• Widely used in literature for multiple tumour sites and with different imaging modalities • Includes errors of over and under-outlining • Benchmark level defined for poor concordance (breast cancer)	• Whole volume metric, may miss areas of variation within the volume • Summary metrics incorporating both over- and under-outlining errors • Concordance will increase with larger volumes • Correlates poorly with length • Failure to detect small but potentially clinical significant anatomical errors such as the bronchus in the SCOPE 1 pre-trial test case • No information on the direction of the error
Geographical Miss Index (GMI)	• Calculates amount of under-outlining	• Calculates amount of geographical miss i.e. under-outlining	• Well correlated with volume • No benchmark for comparison, tumour site and case dependent

Table 1: Detailed Information on Conformity Indices Used in Comparing Radiotherapy Target Volumes [54, 55]

Conformity Indice Name	Description of Metric	Advantages	Disadvantages
Discordance Index (DI)	• Calculates amount of over-outlining	• Calculates amount of over-outlining	• Well correlated with volume • No benchmark for comparison, tumour site and case dependent
Kouwenhoven Index	• Ratio of the volume of overlap of two structures over union volume of the 2 or more structures	• No reference volume required for calculation	• Value dependent on conformity to other investigators and not with gold standard
Kappa Statistic (Fleiss)	• Measurement of magnitude of agreement between multiple outlines	• No reference volume required for calculation • Objective benchmark values to assess agreement	• Value dependent on investigators and not with gold standard • Only valid for multiple investigator outlines • Decision required about what level of agreement is acceptable • No information on the direction of the error

Conformity Indice Name	Description of Metric	Advantages	Disadvantages
Kappa Statistic (Cohen)	• Measurement of magnitude of agreement between two outlines	• Can be used to compare two outlines e.g. investigator volume and reference volume • Objective benchmark values to assess agreement	• Not been previously used to assess outlining variation • Decision required about what level of agreement is acceptable • No information on the direction of the error
Mean Distance to Conformity (MDC)	• Shape based statistic that measures the mean displacement needed to transpose every voxel in the investigator volume onto the reference volume	• Gives measurements of variation (in mm) • Has an over and an under-outlining component • Independent of size of volumes under comparison	• Over and under-outlining MDC values that are high in one direction could cancel each other out • Use of the under and over-outlining MDC results in two metrics, offsetting the advantages of a single metric to describe outlining • No information on the direction of the error • Correlates poorly with length and volume

Inter-observer Variation in the Context of UK Radiotherapy Trials

Now for over a decade the UK's RTTQA group has been instrumental in the administration of quality assurance for national UK radiotherapy trials. Consequently, it has collated a substantial repository of pre-trial benchmark case data from multiple different UK centres participating in multiple different UK radiotherapy trials. Given the growing weight of international evidence highlighting the importance of target volume outlining on patient outcomes this data holds a wealth of important information on the degree of observer variability that exists amongst UK Clinical Oncologists in the context of clinical trials. Work evaluating inter-observer variability in GTV delineation in the context of upper and lower gastro-intestinal (GI) tumour sub-sites has already been conducted thorough the analysis of the SCALOP, ARISTOTLE, NEO-SCOPE and SCOPE 1 pre-trial benchmark case [83-86].

The National Cancer Research Institute SCOPE 1 trial was a phase II/III randomised controlled trial of chemoradiation with capecitabine and cisplatin with or without cetuximab for oesophageal cancer. Prospective trial centres were required to complete a mid-oesophagus pre-trial benchmark case with the help of a comprehensive radiotherapy outlining protocol. A total of 50 investigators drawn gross tumour volumes were received from 34 UK oncology centres and these were analysed against a pre-defined gold standard GTV to determine several different CIs (JCI, GMI, and DI). The SCOPE I data revealed a median JCI for investigator GTV's of 0.69 (interquartile range, 0.62 – 0.70) with 14 of 50 investigators (28%) achieving a JCI of 0.70 or greater [83]. The SCOPE I JCI values were comparable with those published in three different studies who had JCI values ranging between 0.69 – 0.72 [87-89].

Through the course of the SCOPE 1 GTV analysis a new metric termed the local conformity index (L-CI) was established. Unlike traditional CIs which analyses the structure of interest the L-CI analysed the structure on each individual CT slice and can highlight individual CT slices where GTV discordance was greatest [27]. Gwynne et al. found that the highest levels of discordance (<20% of investigators achieving a

L-JCI ≥0.70) was seen on four CT slices and was now able to directly review these slices for an underlying reason. What they found was a mixture of under outlining of the oesophageal wall and inappropriate inclusion of the azygous vein, pericardium, bronchus or peri-bronchial tissues which they concluded was due to misinterpretation of normal anatomy [27].

Normal Tissue Outlining in the Context of UK Radiotherapy Trials

So far, most published research involving UK radiotherapy trials has focused on the extent of inter-observer variation concerning the gross tumour volume [64, 90-93]. Comparatively, much less work has been conducted on inter-observer variability involving normal tissue outlining [22].

Analysis of the SCOPE 1 data revealed that clinicians were misinterpreting normal tissues seen on CT as viable tumour tissue. This raises the question as to the extent of inter-observer variation and radiological misinterpretation which is also taking place when clinicians outline the normal anatomical structures on the CT planning scan. These normal organs can have an important bearing on the radiotherapy planning process as Loo et al. demonstrated when they conducted a systemic review evaluating inter-observer variation in parotid gland delineation and its impact on intensity-modulated radiotherapy solutions [22]. Loo et al. found that almost half of the contours (46%) produced by the participating radiation oncologists and radiologists were sufficiently different from the contour used clinically to have necessitated a different IMRT plan if used [22]. Therefore, bearing in mind the constraints of these normal tissues can dictate the optimal radiotherapy plan selected, poor outlining of normal tissue structures could potentially have a direct impact on the quality and outcome of a patient's treatment.

Assessment of Target Volume and Normal Tissue Structures in The Context of UK Head and Neck and Lung Cancer Radiotherapy Trials

The first hypothesis for this research is that there is a statistically significant inter-observer variation amongst clinical oncologist's target volume and OAR contours

within the context of the pre-trial quality assurance (QA) benchmark cases for four different UK radiotherapy trials. The second hypothesis is that RTQA feedback during the pre-trial benchmark period improves head and neck clinician contouring.

This research tests the first hypothesis by establishing whether any statistically significant inter-observer variation exists amongst UK head and neck and lung cancer oncologists by analysing their target volume and OAR contours submitted via the pre-trial benchmark QA cases.

The second hypothesis has been tested by establishing whether RTQA team feedback significantly impacts on UK head and neck oncologists target volumes and OAR contours during the pre-trial benchmark QA period.

This work will analyse the pre-trial benchmark cases of the ART-DECO, COSTAR, IDEAL and i-START trials. It will also analyse the re-submissions contours from the ART-DECO and COSTAR trials.

Chapter 2: Materials and Methods

Overview of the Head and Neck and Lung Cancer Trials Selected for Analysis

To investigate the degree of inter-observer variability which exists amongst clinical oncology consultants routinely outlining head and neck and lung cancer target and organs at risk volumes four national radiotherapy trials were selected which require clinicians to complete pre-trial outlining benchmark cases. The two head and neck trials selected were the ARTDECO (Accelerated Radiotherapy sTudy of Dose EsCalated intensity-mOdulated radiotherapy versus standard dose intensity-modulated radiotherapy in patients receiving treatment for locally advanced laryngeal and hypopharyngeal cancers) and the COSTAR (COchlear Sparing inTensity modulAted Radiotherapy versus conventional radiotherapy in patients with parotid tumours) trials. The ARTDECO trial is evaluating dose escalated, accelerated (total dose of radiation is given over a shorter period (fewer days) compared to standard radiation therapy), IMRT versus standard dose IMRT in patients receiving treatment for locally advanced laryngeal and hypopharyngeal cancers. The COSTAR trial is evaluating the potential toxicity benefits of cochlear-sparing IMRT versus conventional radiotherapy in patients with parotid tumours.

The two lung cancer trials selected were the IDEAL (Isotoxic Dose Escalation and Acceleration in Lung Cancer ChemoRadiotherapy) and i-START (ISoToxic Accelerated RadioTherapy in locally advanced non-small cell lung cancer) trials. The IDEAL trial was evaluating the toxicity, feasibility and potential clinical effectiveness of isotoxic, dose-escalated radiotherapy with concurrent chemotherapy versus standard chemoradiotherapy in patients with stage II or stage III non-small cell lung cancer (NSCLC). The method of dose escalation in IDEAL was through an individual patient-based model. Each patient would be treated to the dose that, based on the optimised distribution of radiation on his/her treatment plan, was calculated to be associated with an acceptable level of grade three toxicity (from oesophagus or lung). In this way, each patient would be treated to the highest acceptable dose for his/her own situation and would not be exposed to excess risk with the introduction of a generic high-dose to the whole population. This method of

individualised dose escalation using predefined normal tissue constraints is termed isotoxic radiotherapy e.g. one patient receives 66Gy, another 74Gy based upon the maximum safe achievable dose to the patient which remains within the bounds of the pre-defined normal tissue constraints for those critical organs surrounding the target volume. For instance, in thoracic radiotherapy, this includes the mean lung dose (MLD), the oesophagus and the spinal cord.

The i-START trial was designed to determine the highest doses of radiotherapy that could be safely delivered in locally advanced NSCLC and would evaluate the feasibility of delivering isotoxic, accelerated radiotherapy in the treatment of patients with stage II to stage IIIB NSCLC.

Overview of the Pre-Trial Outlining Quality Assurance (QA) Program

For all four trials, normally one consultant clinical oncologist in each participating centre is designated the principle investigator (PI) and it is their duty to act as the local lead for the trial in their centre. All the selected trials required the local PI to complete pre-accrual contouring benchmark cases. The purpose of the benchmark cases was multifactorial. Firstly, to ensure that the PI was correctly following the contouring guidelines contained within each of the trials outlining protocols, secondly to ensure the correct nomenclature was being used to define the volumes and finally to ensure that target volume geometric expansion was done correctly and using reasonable expansion margins.

Trial pre-accrual benchmark cases were available for download from their respective webpage on the Radiotherapy Trials Quality Assurance (RTTQA) website (http://www.rttrialsqa.org.uk/). Each case consisted of a compressed DICOM CT data set. DICOM is an acronym for Digital Imaging and Communications in Medicine which is a standard for handling, storing, printing, and transmitting information in medical imaging. Participating clinicians were instructed to extract and import the DICOM data into their centres radiotherapy treatment planning system (TPS). This allowed the trial PI to complete the outlining cases using the planning software they would normally use to plan their patients. In the case of the IDEAL and i-START trials

clinicians were also able to download the diagnostic PET scans relevant to each of the two cases to assist with target volume delineation.

When completing the contouring cases, PI's were expected to refer to the appropriate trial protocol because it contained a clinical history for each contouring case, diagnostic radiology findings for the cases, definitions of target volumes and critical structures, guidance on delineating target volumes and some normal structures, and guidance on structure naming and nomenclature.

ARTDECO and COSTAR Trial: Outlining QA Program

The ARTDECO trial requires PI's to complete two pre-trial benchmark contouring exercises; the first a squamous cell carcinoma of the larynx case and the second a squamous cell carcinoma of the hypopharynx case. For the COSTAR trial PI's were required to outline a single case which was the post-operative bed and elective nodes of a 53-year-old female who had undergone surgery for a right sided high-grade ex-pleomorphic adenoma of the parotid gland. Both the ARTDECO and COSTAR trial protocols stipulated which target and normal organ structures needed to be contoured.

The ART-DECO target volume delineation and planning guidelines contained anatomical illustrations for each head and neck subsite, nodal atlas, and step-by-step instructions detailing how the GTV, CTV and PTV contours should be constructed. Aside from detailing which normal organs should be contoured for each case (spinal cord, brainstem, contralateral parotid and ipsilateral parotid) no further information regarding delineation was provided.

The COSTAR target volume delineation and planning guidelines also contained illustrations detailing the anatomy of the parotid gland, guidance on nodal outlining, and step-by-step instructions detailing how the parotid bed (CTV) and PTVs should be constructed. Clinicians were instructed to outline both cochlea, contralateral parotid gland, spinal cord (below foramen magnum), brainstem (above foramen magnum) and lens. The COSTAR guidelines included definitions to aid correct outlining of the brainstem and spinal cord; the brainstem was defined as

beginning at the level of the foramen magnum and outlining of the structure should extend sufficiently superior to continue beyond the limit of irradiating fields. The spinal cord was defined as beginning below the level of the foramen magnum and extending inferiorly to the manubrium. Clinicians were also asked to contour the spinal cord and not the spinal canal. Prospective COSTAR PI's were expected to follow these instructions to help standardise spinal cord and brainstem outlines.

Once the prospective PI had completed the benchmark outlining cases for either the ARTDECO or COSTAR trials then their contours were transmitted back to the respective central QA team for that trial. Once received, the trial QA team would perform an assessment of the submitted contours using the trial protocol and the tumour management group's (TMG) reference contours for that benchmark case. The TMG reference contours were consensus contours drawn from the collective agreement of the clinicians who sit on the trial management group. Example images taken from the ARTDECO and COSTAR TMG consensus contours can be seen in Figure 3, Figure 4 and Figure 5.

IDEAL & i-START Trials: Outlining QA Program

The IDEAL and i-START trials both share the same pre-trial benchmark outlining exercises. Again, both trials required prospective PI's to contour two pre-trial benchmark outlining exercises. Both clinical cases were locally advanced, stage III lung cancers with tumours located centrally within the chest. To aid clinicians background case histories, the diagnostic imaging (CT plus PET) with the reports were provided along with the planning CT scan. The IDEAL / i-START outlining instructions requested clinicians to create structures to represent the body, GTV, CTV, PTV, left lung, right lung, the total lung minus the GTV volume, spinal cord, heart and oesophagus. The IDEAL trial planning and delivery guidelines (which the pre-trial benchmark cases advised clinicians to reference) contained target and normal organ delineation instructions. Clinicians were given guidance on how to define the GTV, CTV, PTV, lungs (these should be segmented in every slice from the apex to the base as a paired organ), oesophagus (defined as a solid organ 4cm above and 4cm below the PTV; if a 4cm margin is not possible inferiorly then the

gastro-oesophageal junction will determine the inferior limit of segmentation), spinal cord (defined as the spinal canal 4cm above and 4cm below the PTV) and heart. Prospective trial PI's were therefore expected to follow the guidance contained within the planning and delivery protocol to help standardise target volume and OAR outlining.

As with the ARTDECO and COSTAR trials, once the prospective IDEAL or i-START trial PI had completed the benchmark outlining cases their contours were transmitted back to the IDEAL / i-START QA team for contour analysis. The contour assessment was performed using the trial protocol and the TMG reference contours. Again, the TMG reference contours were contours drawn from the agreement of the clinicians who sit on the trial management group. Both the IDEAL and i-START trials had their own reference contours for prospective PI contour analysis. Example images taken from the IDEAL TMG consensus contours can be seen in Figure 6 and Figure 7.

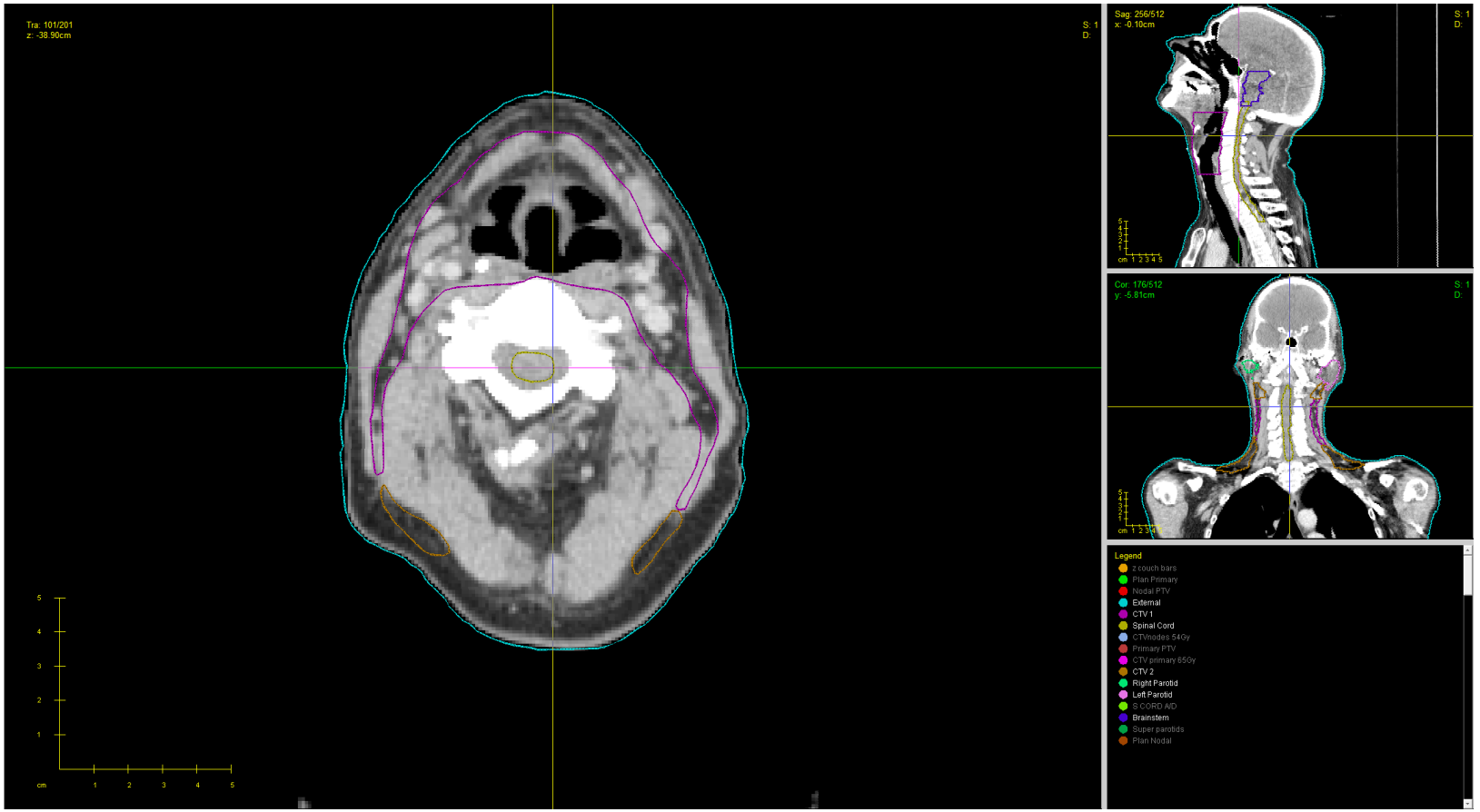


Figure 3: Example CT Slice from ARTDECO Contouring Exercise 1 Displaying TMG Reference Contours (turquoise = body contour; light purple = CTV1 (high dose volume); brown = CTV2 (low dose volume); yellow = spinal cord; green = right parotid gland; pink = left parotid gland; dark purple = brainstem).

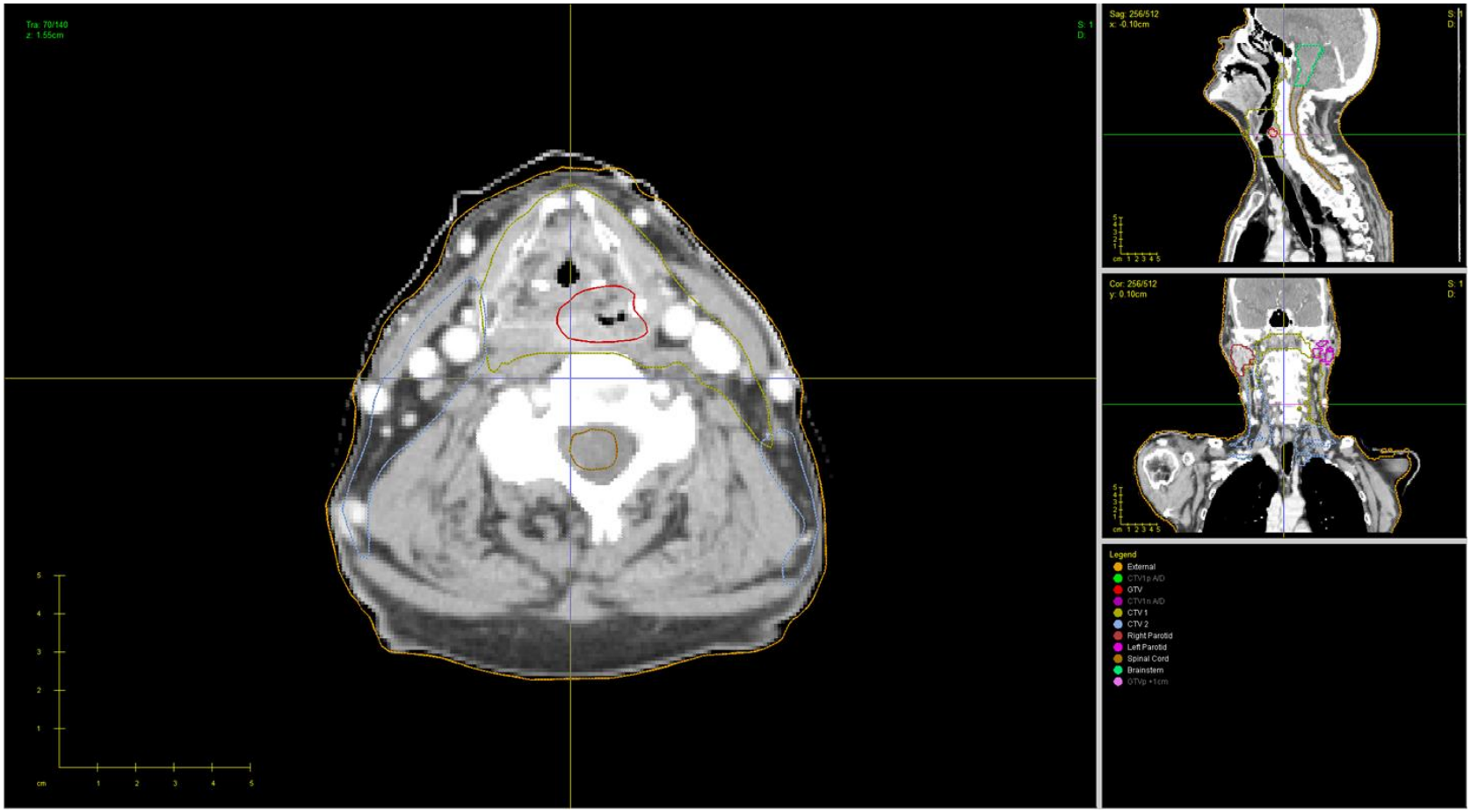


Figure 4: Example CT Slice from ARTDECO Contouring Exercise 2 Displaying TMG Reference Contours (orange = body contour; dark red = GTV; yellow = CTV1 (high dose volume); light blue = CTV2 (low dose volume); light red = right parotid gland; purple = left parotid gland; brown = spinal cord; green = brainstem)

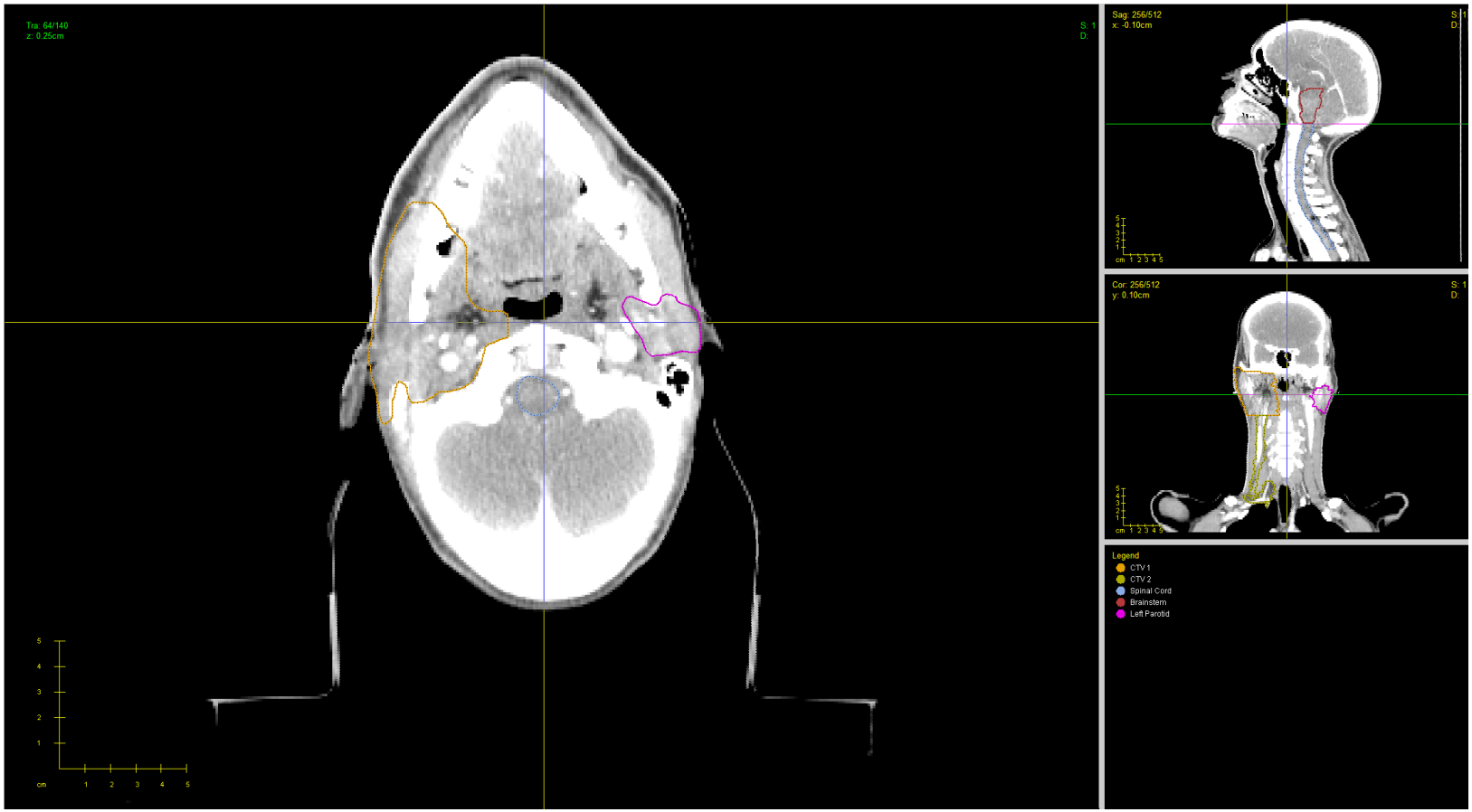


Figure 5: Example CT Slice from COSTAR Contouring Exercise Displaying TMG Reference Contours (orange = CTV1 (high dose volume); yellow = CTV2 (low dose volume); blue = spinal cord; purple = left parotid gland; red = brainstem)

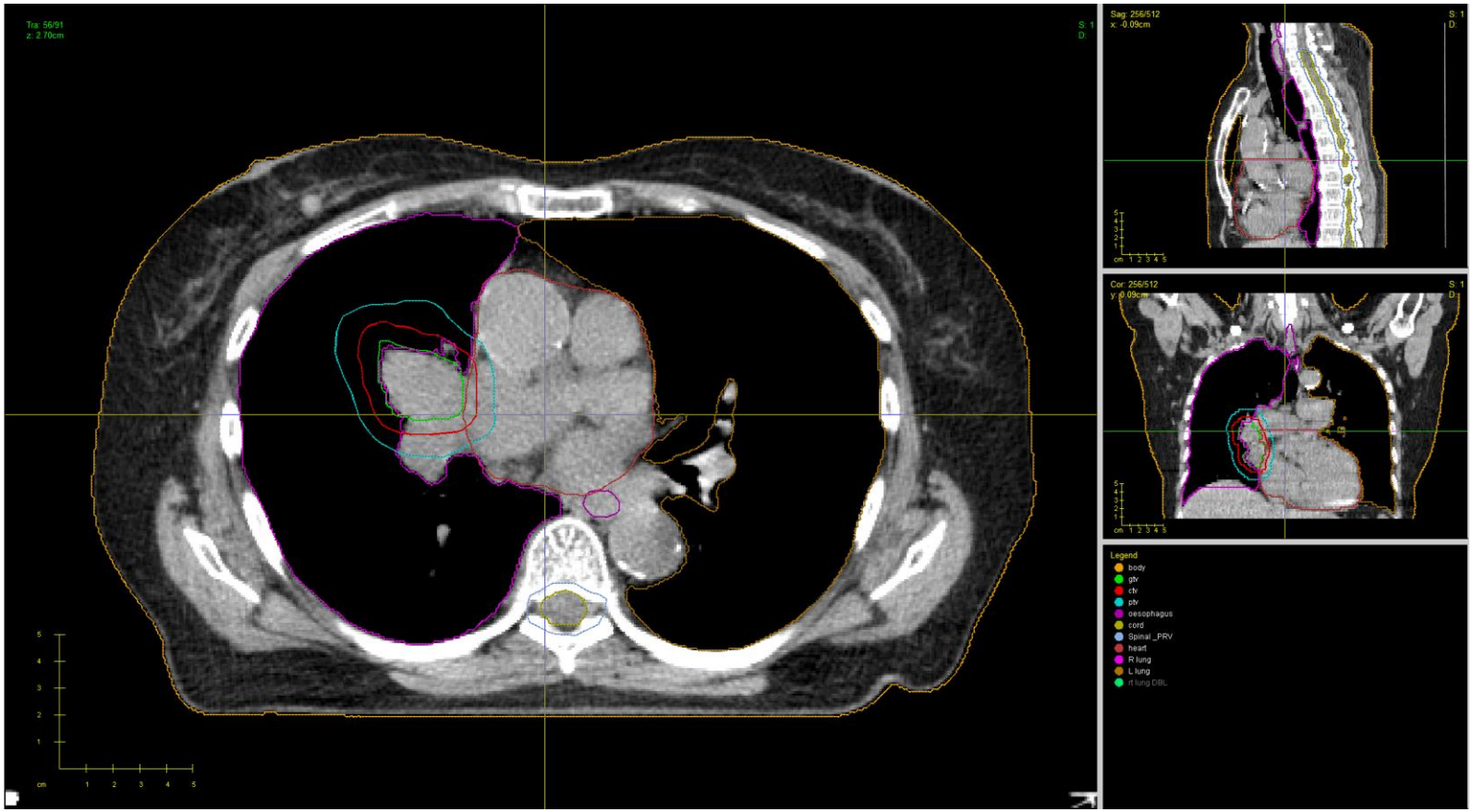


Figure 6: Example CT Slice from IDEAL / i-START Contouring Exercise 1 Displaying IDEAL Reference Contours (dark yellow = body; green = GTV, dark red = CTV, turquoise = PTV; dark purple = oesophagus; light yellow = spinal cord; blue = spinal cord PRV; light red = heart; light purple = right lung; brown = left lung)

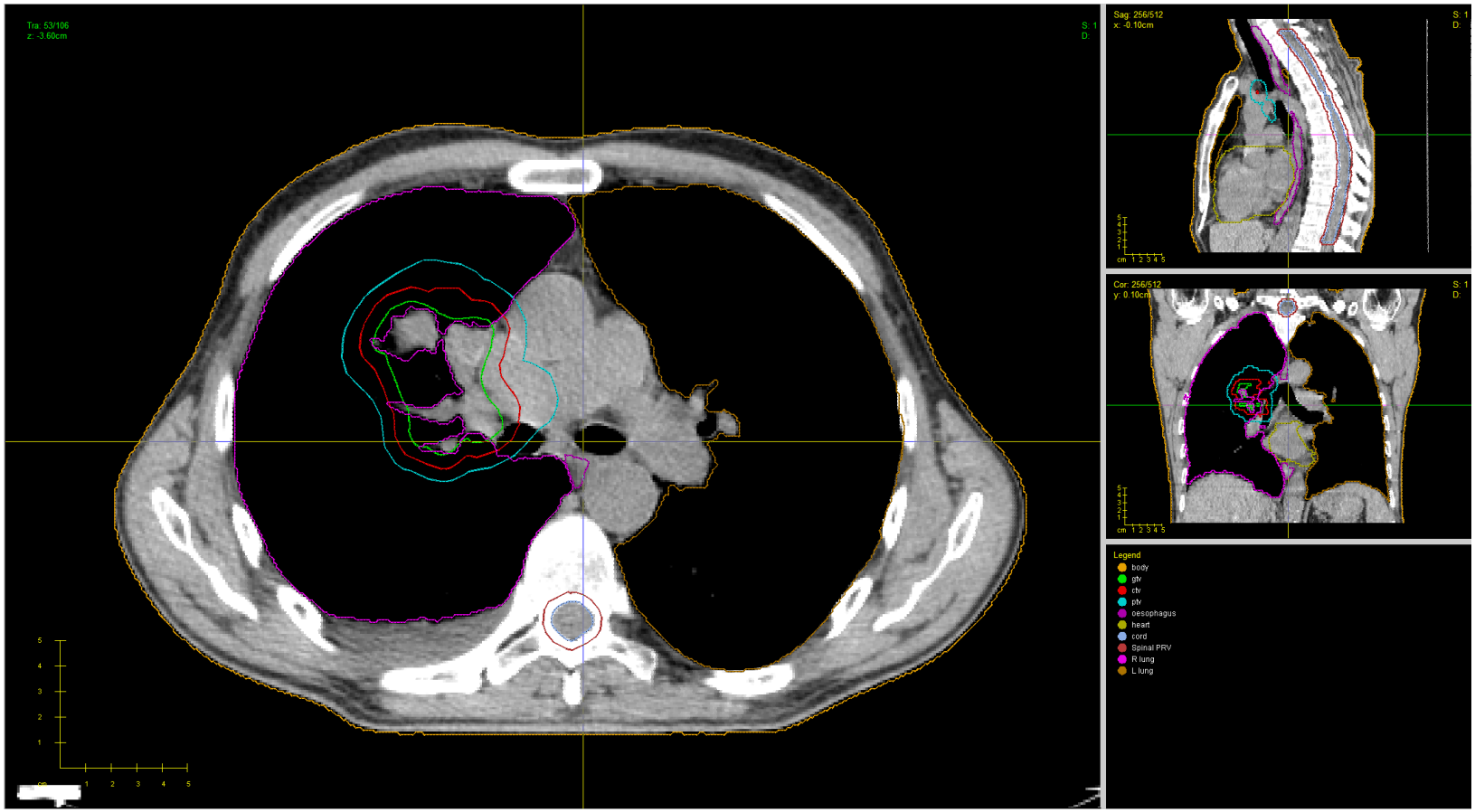


Figure 7: Example CT Slice from IDEAL / i-START Contouring Exercise 2 Displaying IDEAL Reference Contours (dark yellow = body; green = GTV, dark red = CTV, turquoise = PTV; dark purple = oesophagus; light yellow = heart; blue = spinal cord PRV; light red = spinal cord PRV; light purple = right lung; brown = left lung)

Overview of the Assessment Process Used in the Pre-Trial QA Program

All pre-trial outlining benchmark exercises submitted for assessment were first reviewed by the respective trials QA team for trial protocol outlining compliance. The TMG's reference contours were then used as a visual benchmark to assess whether the contours submitted adequately delineated the target volumes and OARs stipulated in the contouring exercise instructions.

In the context of the head and neck trials, if the RTQA team felt that the target volumes or OAR structures were unsatisfactory due to deviations from the outlining protocol, then the submitting clinician was requested to resubmit their contours following guidance set out in the RTQA team's feedback report. Once resubmitted, the cases were then re-reviewed for protocol compliance and further resubmissions requested until judged trial protocol compliant. An analysis of the impact of this on clinician outlining can be found in Chapter 5.

Data Analysis Step 1: Data Collection and Processing

I collected all benchmark cases, including resubmissions, for ARTDECO and COSTAR up until June 2012 in DICOM format. For the IDEAL and i-START trials, I collected all submitted benchmark cases in DICOM format up until November 2012.

Before any of the submitted DICOM data could be analysed all the structure names contained within the submitted cases had to manually checked and edited by me to ensure consistent structure naming; approximately 1000 individual structures in total.

This time-consuming step was necessary because the conformity analysis tool required all the same structures to be labelled in the same way i.e. 'CTV1' and not 'CTV_1' or 'CTV-1'; 'Brainstem' and not 'Brain_Stem' or 'BS'. Without me performing this important step the analysis tools would not have been able to analyse all the submitted structure contours as it would not have recognised many of them due to inconsistent structure nomenclature.

Data Analysis Step 2: Analysis of Pre-Trial Benchmark Cases

Once the data had been processed to ensure uniform structure nomenclature it was then analysed using a conformity analysis tool built by Dr Emiliano Spezi using MATLAB R2011a and CERR v.4.0 by. All submitted cases were analysed against their respective trial management group (TMG) consensus contours to assess for inter-observer and intra-observer variation. The conformity analysis tool calculated the volume of each structure then the Dice coefficient (DC), Jaccard index (JI), geographical miss index (GMI) and RIET index for each structure by comparing it directly to its comparative TMG reference structure. To facilitate easy comparison of all 4 output indices, 1-GMI was also calculated.

The conformity analysis tool also calculated the Local Conformity Index (L-CI) for each structure. This metric was created following analysis of the SCOPE 1 pre-trial benchmark case GTV structures. Unlike traditional conformity indices which analyses the structure of interest the L-CI analyses the structure on each individual CT slice and can help highlight where discordance is greatest within each contoured structure on an individual CT slice basis.

Data Analysis Step 3: Collation of Output Structure Analysis Data

Once the conformity analysis tool had finished calculating the data it was output as comma-separated values files (.CSV files) which Microsoft Excel 2016 recognises as a single column of numerical values contained within a spreadsheet with each row within the Excel spreadsheet representing a different submitting clinician. The analysis tools created a .CSV file for every indice measured for every structure analysed. In total 1609 individual .CSV files were created for all the structures analysed. For the purposes of further analysis, I collated the data from each .CSV file into Microsoft Excel 2016 spreadsheets.

To permit statistical analysis of inter-observer variation within the output data, the analysed head and neck trial and lung trial structures were grouped into three different categories:

1. Targets (which included CTVs)
2. Serial OARs (which included spinal cord, brainstem and oesophagus)
3. Parallel OARs (which included parotid glands, heart and lungs)

Data Analysis Step 4: Statistical Analysis of the Conformity Indice Data

Once all the data had been collated in Excel 2016, it was then analysed using MATLAB to look for statistically significant differences to determine whether the proposed hypotheses were valid.

Submission structures from all the trials were sorted into three distinct groups – target structures (which included the high dose CTV); serial organs at risk (which included spinal cord, brainstem and oesophagus) and parallel organs at risk (which included the parotid glands, lungs and heart). The organs contained within each respective serial or parallel group were determined using the radiobiological definitions of parallel and serial organs. The term parallel organ is based upon an analogy with electrical circuits and can be contrasted with serial organs. A parallel organ, like the parotid gland, has redundancy built in, and a certain fraction of the organ parenchyma (or functional subunits) can be sacrificed and the organ will still maintain its function albeit reduced. Classic serial organs are the spinal cord and oesophagus where loss of function will occur if even a small length of either structure is sacrificed; typically, serial organs are tubular structures and therefore cylindrical in shape.

Using these definitions, the target structure group contained the volumes which clinicians had defined as containing either the primary tumour, or areas at high risk of containing residual tumour cells. The parallel organs at risk group contained those critical organs which are defined within the context of radiotherapy planning as being parallel i.e. parotid glands, lungs and heart (although the heart organ does contain serial tissues and can therefore be considered a serial-parallel organ). The serial organs at risk group contained critical organs which are defined within the context of radiotherapy planning as being serial i.e. spinal cord, brainstem and oesophagus. Parallel and serial organs also differ geometrically as serial organs are

normally tubular shaped structures whereas parallel organs are often more complex in their anatomical shape. Therefore, the organ at risk groupings used for the purposes of analysis could be considered to reflect those with more complex 3D structures (parallel organs) and those with simpler tubular shapes (serial organs).

For hypothesis one this was tested using a paired difference test with Bonferroni correction. A paired difference test is a type of location test that is used when comparing two sets of measurements to assess whether their population means differ. A paired difference test uses additional information about the sample that is not present in an ordinary unpaired testing situation, either to increase the statistical power, or to reduce the effects of confounders. A Bonferroni correction was utilised to counteract the problem of multiple comparisons. The results of these analyses are detailed in Chapters 3 and 4.

For hypothesis two, a paired t-test was utilised. A paired t-test is a statistical technique that is used to compare two population means in the case of two samples that are correlated. This test seemed most appropriate for detecting possible statistical differences between the first and final contouring submissions.

Data Analysis Step 5: Designing an Innovative Solution for Collating L-CI Structure L-Data

In the case of the structure L-CI data, because of its complex nature an innovative method of consolidating it was needed which would allow an easy and rapid visual interpretation of its findings. My solution to this problem was to create a bespoke spreadsheet for each structure analysed from each benchmark case using Microsoft Excel 2016. How this was done is detailed in Appendix 1 and by using this method, it was then possible to quickly visualise where the greatest variation existed in clinician target and OAR contouring and therefore useful in interpreting the individual Dice, Jaccard, Van't Riet and GMI indices and the statistical analysis of their findings.

Chapter 3: Results of Inter-Observer Variation Analysis Between Target Volume, Serial and Parallel OAR Outlines Within Two Head and Neck Clinical Trials

I collected all the pre-trial benchmark cases for the ARTDECO and COSTAR trials up until June 2012 in DICOM format. In total 288 first submission structures were analysed from both trials based upon three distinct groups – target structures (which included the high dose CTV); serial organs at risk which (included spinal cord and brainstem) and parallel organs at risk (which included parotid gland). Details of these grouping are summarised in Table 2 below.

Group Name	Structures Included in Group	Number of Structures Analysed	Total
Target Structures (TARGET)	CTV1 (high dose CTV)	63	63
Serial Organs (OAR-S)	Spinal Cord	63	126
	Brainstem	63	
Parallel Organs (OAR-P)	Left Parotid	63	99
	Right Parotid	36	

Table 2: Summary of COSTAR and ARTDECO Target and OAR Contour Groupings

Descriptive statistics are summarised for the DICE, JACCARD, RIET and 1-GMI indices for each respective group in Table 3. The mean index value shown in column two of Table 3 is the numerical measure of conformity for each indice analysed. This is a numerical scale between 1.0 and 0 where 1.0 represents perfect conformity and 0 no conformity. Hence the closer the mean index value is to 1.0 the better the conformity between the structures analysed and conversely, the closer to 0 the worse the conformity.

The boxplot as shown in Figure 8 demonstrates that overall it seems the target contours (CTV1 – which contained the high dose CTV) had the highest conformality, followed by the serial organs at risk (spinal cord and brainstem) and then finally the parallel organs at risk (parotid glands) for all four conformity indices measured.

		Number of contours	Mean Index Value	Standard Deviation	95% Confidence Interval for Mean	
					Lower Bound	Upper Bound
DICE	Target	63	0.80	0.08	0.78	0.82
	Serial Organs	126	0.73	0.12	0.71	0.76
	Parallel Organs	99	0.74	0.09	0.72	0.76
	Total	288	0.75	0.11	0.74	0.76
JACCARD	Target	63	0.67	0.10	0.64	0.69
	Serial Organs	126	0.59	0.13	0.57	0.62
	Parallel Organs	99	0.59	0.11	0.57	0.61
	Total	288	0.61	0.12	0.60	0.62
RIET	Target	63	0.65	0.10	0.62	0.67
	Serial Organs	126	0.57	0.13	0.54	0.59
	Parallel Organs	99	0.56	0.12	0.54	0.59
	Total	288	0.58	0.13	0.57	0.60
1-GMI	Target	63	0.78	0.13	0.74	0.81
	Serial Organs	126	0.77	0.16	0.74	0.80
	Parallel Organs	99	0.71	0.12	0.69	0.74
	Total	288	0.75	0.14	0.74	0.77

Table 3: Summary of descriptive statistics for the DICE, JACCARD, RIET and 1-GMI for OAR-P (parotid glands), OAR-S (spinal cord and brainstem) and TARGET (high dose CTV1)

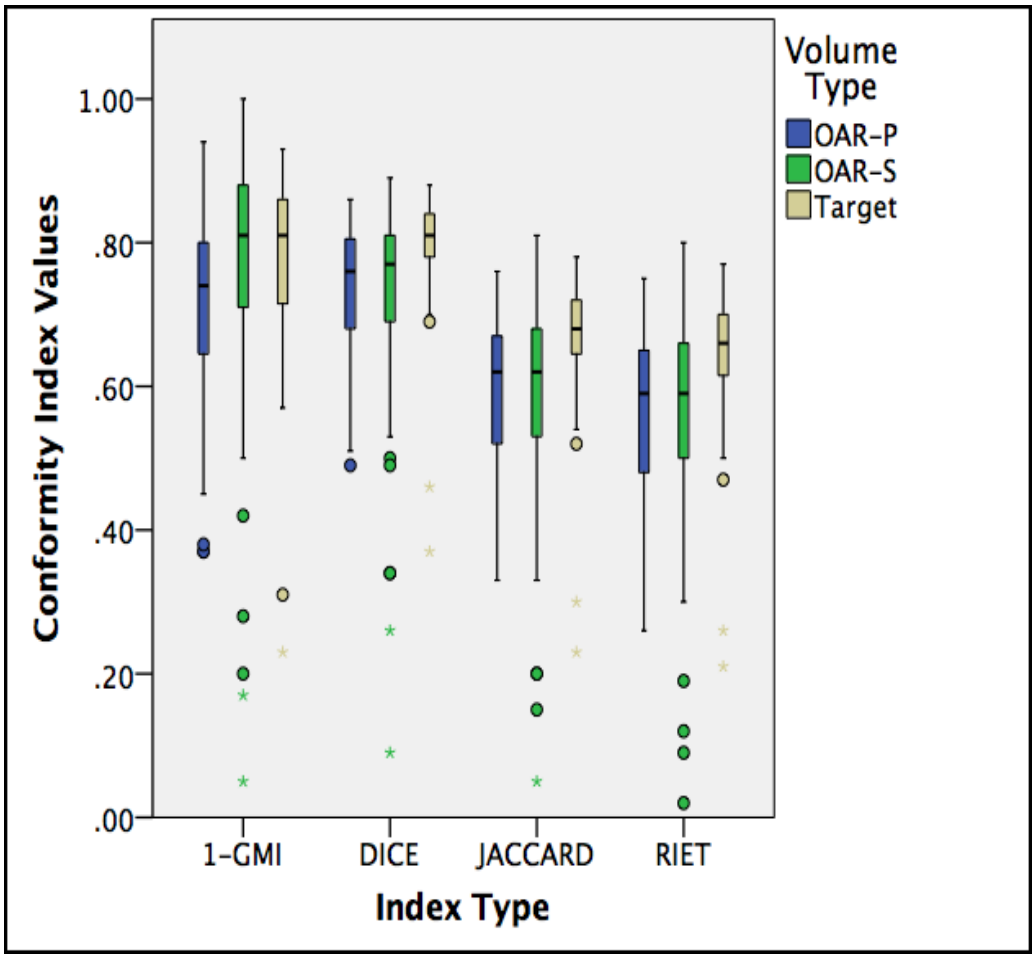


Figure 8: A boxplot displaying the distribution of the DICE, JACCARD, RIET and 1-GMI for OAR-P (parotid glands), OAR-S (spinal cord and brainstem) and TARGET (high dose CTV1)

A pairwise comparison with Bonferroni correction was performed on each of the groups for each conformity indice (DICE, JACCARD, RIET and 1-GMI). The analysis revealed the following statistical differences between each group and indice analysed:

DICE

A significant difference was found between Target and OAR-S ($p<0.05$)
A significant difference was found between Target and OAR-P ($p<0.05$)
No significant difference was found between OAR-S and OAR-P ($p=1.00$)

JACCARD

A significant difference was found between Target and OAR-S ($p<0.05$)
A significant difference was found between Target and OAR-P ($p<0.05$)
No significant difference was found between OAR-S and OAR-P ($p=1.00$)

RIET

A significant difference was found between Target and OAR-S ($p<0.05$)
A significant difference was found between Target and OAR-P ($p<0.05$)
No significant difference was found between OAR-S and OAR-P ($p=1.00$)

1-GMI

No significant difference was found between Target and OAR-S ($p=1.00$)
A significant difference was found between Target and OAR-P ($p<0.05$)
A significant difference was found between OAR-S and OAR-P ($p<0.05$)

To summarise, a statistically significant difference was detected for the DICE, JACCARD and RIET indices when the target volume contours (TARGET) were

compared with both the serial and parallel organ at risk contours (OAR-S and OAR-P).

There was no statistical difference for the DICE, JACCARD and RIET indices when the serial and parallel organ at risk contours were compared with each other (OAR-S and OAR-P).

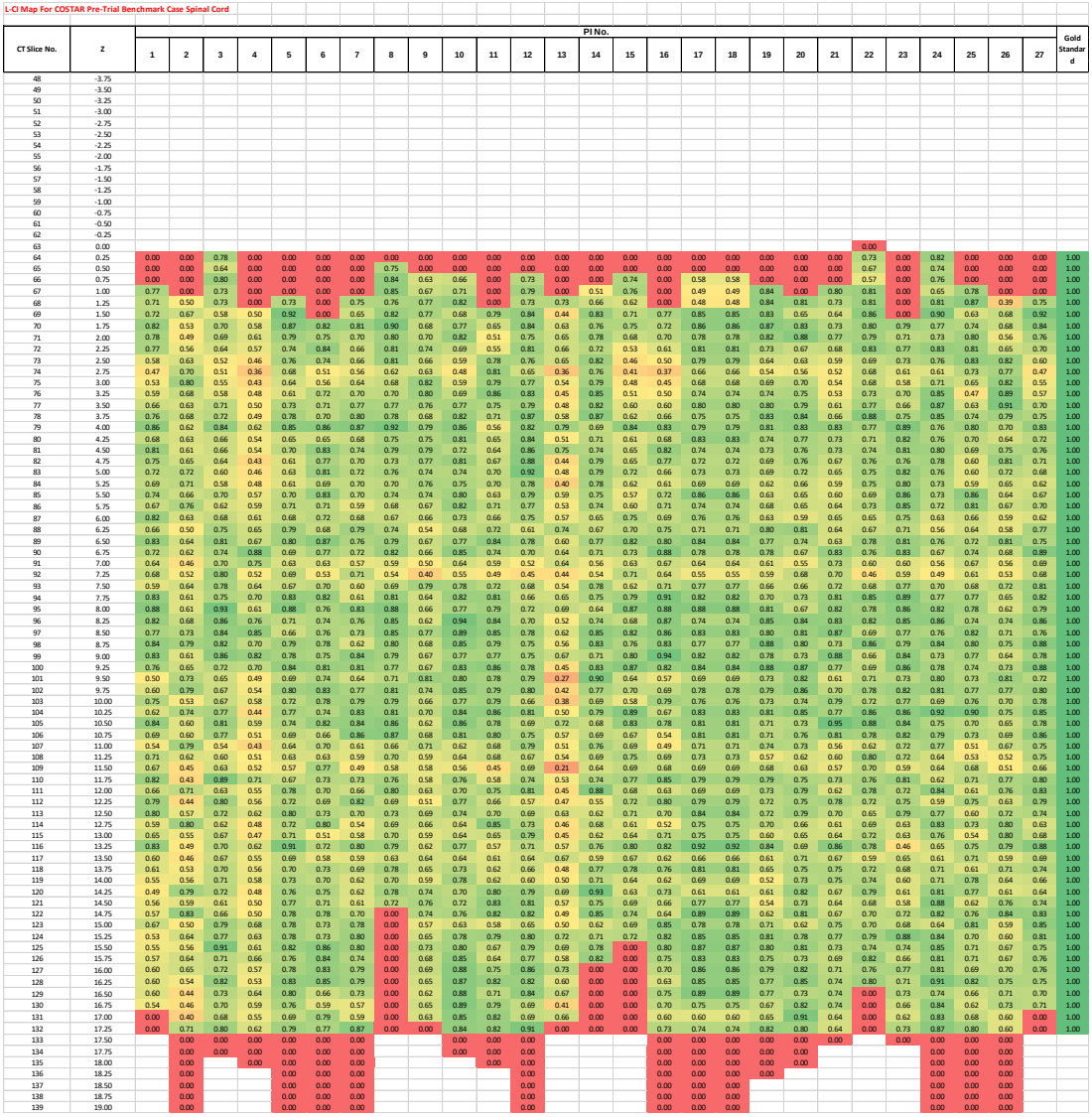
For the 1-GMI indice, there was no statistically significant difference between the target contours (TARGET) and serial organ at risk contours (OAR-S). There was a statistically significant difference between the target contours (TARGET) and parallel organ at risk contours (OAR-P). Finally, there was also a statistically significant difference between the serial and parallel organ at risk contours (OAR-S and OAR-P).

The local conformity index (L-CI) data maps for each of the structures contained within each group can also be seen in Figure 9 – Figure 12. An explanation of how the data was created and should be interpreted can be found in Appendix 1. The DICE, JACCARD, RIET and 1-GMI indices are single metrics of conformity and therefore condense and obscure the over, under and sometimes subtle differences that exist between clinician contours. The L-CI data maps on the other hand help to maintain this level of detail and permit a visual interpretation of it. The L-CI data maps for the ART-DECO and COSTAR target volume and OAR structures demonstrate where the highest and lowest levels of conformity exist and clearly reveal those areas of over and under outlining within each submitted target and OAR structure. The value of L-CI will be discussed in more detail in the resubmission data analysis section of Chapter 6: Discussion.

L-CI Map For ART-DECO Pre-Trial Benchmark Case 2 CTV1

CT Slice No.	z	PI No.																		Gold Standard
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
27	-9.2																			
28	-8.95																			
29	-8.7																			
30	-8.45										0.00									
31	-8.2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.63	0.42	0.70	0.00	0.00	0.48	0.00	0.00	0.00	0.00	1.00
32	-7.95	0.00	0.00	0.25	0.00	0.00	0.00	0.00	0.73	0.67	0.39	0.50	0.00	0.00	0.50	0.60	0.00	0.00	0.00	1.00
33	-7.7	0.68	0.00	0.23	0.00	0.00	0.00	0.00	0.63	0.66	0.46	0.45	0.00	0.00	0.49	0.69	0.00	0.00	0.00	1.00
34	-7.45	0.62	0.55	0.32	0.00	0.00	0.00	0.29	0.72	0.53	0.66	0.75	0.63	0.63	0.46	0.72	0.60	0.65	0.00	1.00
35	-7.2	0.58	0.60	0.41	0.21	0.00	0.00	0.37	0.69	0.55	0.67	0.76	0.66	0.66	0.45	0.66	0.53	0.65	0.00	1.00
36	-6.95	0.53	0.65	0.56	0.64	0.00	0.00	0.26	0.58	0.37	0.74	0.59	0.55	0.55	0.62	0.50	0.58	0.52	0.00	1.00
37	-6.7	0.55	0.66	0.58	0.65	0.61	0.00	0.37	0.54	0.36	0.72	0.70	0.52	0.52	0.60	0.63	0.63	0.51	0.00	1.00
38	-6.45	0.60	0.53	0.53	0.61	0.63	0.00	0.40	0.45	0.34	0.74	0.78	0.55	0.55	0.62	0.80	0.74	0.58	0.00	1.00
39	-6.2	0.75	0.56	0.62	0.71	0.70	0.00	0.44	0.53	0.41	0.72	0.70	0.65	0.65	0.68	0.80	0.73	0.68	0.00	1.00
40	-5.95	0.67	0.54	0.67	0.61	0.63	0.00	0.47	0.55	0.40	0.70	0.63	0.51	0.51	0.67	0.72	0.70	0.71	0.00	1.00
41	-5.7	0.69	0.56	0.62	0.69	0.69	0.00	0.46	0.54	0.42	0.72	0.73	0.58	0.58	0.67	0.76	0.73	0.70	0.00	1.00
42	-5.45	0.64	0.54	0.64	0.62	0.65	0.00	0.46	0.54	0.35	0.71	0.72	0.59	0.59	0.66	0.72	0.70	0.71	0.00	1.00
43	-5.2	0.55	0.52	0.66	0.58	0.59	0.00	0.46	0.48	0.28	0.68	0.68	0.50	0.50	0.66	0.73	0.76	0.65	0.00	1.00
44	-4.95	0.41	0.48	0.52	0.57	0.50	0.00	0.28	0.36	0.29	0.51	0.55	0.48	0.48	0.46	0.71	0.53	0.47	0.00	1.00
45	-4.7	0.43	0.54	0.53	0.65	0.46	0.16	0.26	0.32	0.27	0.44	0.48	0.38	0.38	0.47	0.64	0.46	0.35	0.00	1.00
46	-4.45	0.55	0.55	0.55	0.65	0.59	0.23	0.23	0.26	0.29	0.47	0.48	0.44	0.44	0.38	0.54	0.45	0.37	0.00	1.00
47	-4.2	0.54	0.57	0.55	0.64	0.65	0.33	0.31	0.67	0.23	0.42	0.63	0.44	0.44	0.54	0.51	0.46	0.36	0.21	1.00
48	-3.95	0.49	0.63	0.54	0.68	0.65	0.40	0.38	0.69	0.19	0.39	0.67	0.41	0.41	0.59	0.51	0.55	0.34	0.40	1.00
49	-3.7	0.60	0.54	0.63	0.68	0.66	0.36	0.64	0.76	0.39	0.54	0.68	0.42	0.42	0.73	0.59	0.71	0.43	0.40	1.00
50	-3.45	0.66	0.54	0.64	0.71	0.69	0.38	0.66	0.77	0.40	0.67	0.70	0.75	0.75	0.71	0.59	0.69	0.48	0.45	1.00
51	-3.2	0.65	0.57	0.70	0.73	0.71	0.41	0.69	0.81	0.45	0.73	0.69	0.76	0.77	0.57	0.58	0.72	0.48	0.49	1.00
52	-2.95	0.68	0.56	0.68	0.69	0.56	0.42	0.69	0.74	0.48	0.70	0.68	0.76	0.76	0.51	0.53	0.63	0.49	0.48	1.00
53	-2.7	0.74	0.54	0.68	0.65	0.60	0.46	0.75	0.77	0.50	0.72	0.70	0.79	0.78	0.53	0.58	0.66	0.52	0.47	1.00
54	-2.45	0.71	0.51	0.67	0.64	0.60	0.49	0.78	0.75	0.52	0.72	0.76	0.77	0.75	0.53	0.58	0.62	0.52	0.48	1.00
55	-2.2	0.68	0.49	0.72	0.63	0.58	0.47	0.75	0.56	0.52	0.60	0.55	0.63	0.61	0.54	0.53	0.74	0.54	0.47	1.00
56	-1.95	0.64	0.47	0.69	0.65	0.56	0.52	0.66	0.58	0.56	0.61	0.60	0.65	0.63	0.59	0.55	0.68	0.56	0.51	1.00
57	-1.7	0.86	0.63	0.76	0.74	0.81	0.63	0.87	0.84	0.81	0.78	0.83	0.79	0.79	0.76	0.79	0.79	0.69	0.69	1.00
58	-1.45	0.86	0.68	0.75	0.79	0.82	0.65	0.79	0.86	0.86	0.81	0.84	0.80	0.79	0.78	0.83	0.77	0.71	0.76	1.00
59	-1.2	0.84	0.67	0.77	0.75	0.83	0.66	0.78	0.84	0.84	0.79	0.85	0.78	0.78	0.78	0.85	0.74	0.71	0.76	1.00
60	-0.95	0.85	0.69	0.77	0.77	0.72	0.70	0.83	0.70	0.69	0.79	0.80	0.76	0.76	0.85	0.87	0.84	0.74	0.72	1.00
61	-0.7	0.84	0.75	0.62	0.82	0.73	0.72	0.81	0.73	0.69	0.80	0.82	0.76	0.76	0.82	0.74	0.80	0.77	0.75	1.00
62	-0.45	0.85	0.81	0.75	0.82	0.81	0.63	0.76	0.77	0.72	0.76	0.62	0.77	0.77	0.77	0.84	0.63	0.63	0.73	1.00
63	-0.2	0.82	0.80	0.74	0.81	0.83	0.63	0.78	0.84	0.73	0.74	0.66	0.82	0.82	0.72	0.84	0.60	0.64	0.75	1.00
64	0.05	0.89	0.81	0.77	0.86	0.87	0.74	0.78	0.86	0.79	0.77	0.83	0.84	0.83	0.78	0.84	0.62	0.69	0.81	1.00
65	0.3	0.90	0.77	0.76	0.82	0.88	0.77	0.79	0.86	0.85	0.75	0.81	0.82	0.80	0.78	0.91	0.75	0.84	0.82	1.00
66	0.55	0.90	0.80	0.74	0.82	0.82	0.73	0.74	0.86	0.88	0.77	0.81	0.81	0.80	0.84	0.91	0.78	0.84	0.84	1.00
67	0.8	0.87	0.79	0.74	0.79	0.82	0.78	0.72	0.86	0.83	0.74	0.82	0.75	0.74	0.84	0.92	0.77	0.81	0.85	1.00
68	1.05	0.90	0.82	0.77	0.83	0.83	0.81	0.76	0.86	0.85	0.76	0.84	0.79	0.77	0.83	0.93	0.82	0.83	0.86	1.00
69	1.3	0.87	0.75	0.74	0.81	0.86	0.81	0.77	0.85	0.84	0.75	0.78	0.83	0.82	0.86	0.89	0.81	0.83	0.87	1.00
70	1.55	0.87	0.78	0.76	0.83	0.86	0.81	0.79	0.83	0.84	0.77	0.74	0.79	0.78	0.90	0.88	0.84	0.86	0.84	1.00
71	1.8	0.88	0.75	0.75	0.83	0.89	0.85	0.78	0.81	0.81	0.78	0.75	0.78	0.78	0.89	0.88	0.84	0.85	0.80	1.00
72	2.05	0.87	0.79	0.73	0.81	0.87	0.83	0.75	0.85	0.81	0.77	0.80	0.81	0.84	0.89	0.87	0.87	0.86	0.81	1.00
73	2.3	0.89	0.75	0.73	0.82	0.88	0.82	0.74	0.81	0.80	0.76	0.74	0.80	0.81	0.87	0.91	0.85	0.86	0.79	1.00
74	2.55	0.87	0.83	0.71	0.81	0.86	0.84	0.76	0.81	0.78	0.79	0.78	0.85	0.83	0.84	0.90	0.87	0.86	0.83	1.00
75	2.8	0.84	0.80	0.72	0.82	0.88	0.86	0.73	0.74	0.76	0.82	0.76	0.82	0.82	0.85	0.89	0.84	0.83	0.79	1.00
76	3.05	0.83	0.76	0.72	0.77	0.86	0.83	0.74	0.74	0.81	0.78	0.76	0.80	0.78	0.82	0.89	0.81	0.83	0.78	1.00
77	3.3	0.82	0.75	0.75	0.73	0.86	0.84	0.75	0.73	0.83	0.80	0.74	0.78	0.77	0.84	0.90	0.81	0.83	0.77	1.00
78	3.55	0.83	0.75	0.70	0.69	0.81	0.89	0.82	0.74	0.87	0.72	0.74	0.80	0.80	0.85	0.90	0.84	0.82	0.59	1.00
79	3.8	0.80	0.75	0.64	0.67	0.74	0.84	0.78	0.78	0.88	0.74	0.78	0.75	0.76	0.82	0.89	0.84	0.82	0.58	1.00
80	4.05	0.78	0.76	0.62	0.63	0.67	0.76	0.79	0.74	0.87	0.72	0.76	0.75	0.74	0.84	0.90	0.85	0.84	0.00	1.00
81	4.3	0.70	0.82	0.53	0.66	0.00	0.67	0.00	0.69	0.85	0.66	0.73	0.00	0.00	0.00	0.86	0.78	0.84	0.00	1.00
82	4.55	0.67	0.00	0.31	0.20	0.00	0.54	0.00	0.42	0.00	0.61	0.00	0.00	0.00	0.00	0.87	0.80	0.85	0.00	1.00
83	4.8								0.00								0.00			
84	5.05								0.00								0.00			
85	5.3								0.00								0.00			
86	5.55																			
87	5.8																			
88	6.05																			

Figure 9: L-CI Map for ART-DECO Pre-Trial Benchmark Case 2 CTV1 (No Conformity i.e. contour not present (L-CI = 0.00); Poor conformity; Good conformity; Perfect conformity (L-CI = 1.00))



L-CI Map For COSTAR Pre-Trial Benchmark Case Spinal Cord

CT Slice No.	z	PI No.																										Gold Standard
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
48	-3.75																												
49	-3.50																												
50	-3.25																												
51	-3.00																												
52	-2.75																												
53	-2.50																												
54	-2.25																												
55	-2.00																												
56	-1.75																												
57	-1.50																												
58	-1.25																												
59	-1.00																												
60	-0.75																												
61	-0.50																												
62	-0.25																												
63	0.00																						0.00						
64	0.25	0.00	0.00	0.78	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.73	0.00	0.82	0.00	0.00	0.00	1.00
65	0.50	0.00	0.00	0.64	0.00	0.00	0.00	0.00	0.75	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.67	0.00	0.74	0.00	0.00	0.00	1.00
66	0.75	0.00	0.00	0.80	0.00	0.00	0.00	0.00	0.84	0.63	0.66	0.00	0.73	0.00	0.00	0.74	0.00	0.58	0.58	0.00	0.00	0.00	0.57	0.00	0.76	0.00	0.00	0.00	1.00
67	1.00	0.77	0.00	0.73	0.00	0.00	0.00	0.00	0.85	0.67	0.71	0.00	0.79	0.00	0.51	0.76	0.00	0.49	0.49	0.84	0.00	0.80	0.81	0.00	0.65	0.78	0.00	0.00	1.00
68	1.25	0.71	0.50	0.73	0.00	0.73	0.00	0.75	0.76	0.77	0.82	0.00	0.73	0.73	0.66	0.62	0.00	0.48	0.48	0.84	0.81	0.73	0.81	0.00	0.81	0.87	0.39	0.75	1.00
69	1.50	0.72	0.67	0.58	0.50	0.92	0.00	0.65	0.82	0.77	0.68	0.79	0.84	0.44	0.83	0.71	0.77	0.85	0.85	0.83	0.65	0.64	0.86	0.00	0.90	0.63	0.68	0.92	1.00
70	1.75	0.82	0.53	0.70	0.58	0.87	0.82	0.81	0.90	0.68	0.77	0.65	0.84	0.63	0.76	0.75	0.72	0.86	0.86	0.87	0.83	0.73	0.80	0.79	0.77	0.74	0.68	0.84	1.00
71	2.00	0.78	0.49	0.69	0.61	0.79	0.75	0.70	0.80	0.70	0.82	0.51	0.75	0.65	0.78	0.68	0.70	0.78	0.78	0.82	0.88	0.77	0.79	0.71	0.73	0.80	0.56	0.76	1.00
72	2.25	0.77	0.56	0.64	0.57	0.74	0.84	0.66	0.81	0.74	0.69	0.55	0.81	0.66	0.72	0.53	0.61	0.81	0.81	0.73	0.67	0.68	0.83	0.77	0.83	0.81	0.65	0.70	1.00
73	2.50	0.58	0.63	0.52	0.46	0.76	0.74	0.66	0.81	0.66	0.59	0.78	0.76	0.65	0.82	0.46	0.50	0.79	0.79	0.64	0.63	0.59	0.69	0.73	0.76	0.83	0.82	0.60	1.00
74	2.75	0.47	0.70	0.51	0.36	0.68	0.51	0.56	0.62	0.63	0.48	0.81	0.65	0.36	0.76	0.41	0.37	0.66	0.66	0.54	0.56	0.52	0.68	0.61	0.61	0.73	0.77	0.47	1.00
75	3.00	0.53	0.80	0.55	0.43	0.64	0.56	0.64	0.68	0.82	0.59	0.79	0.77	0.54	0.79	0.48	0.45	0.68	0.68	0.69	0.70	0.54	0.68	0.58	0.71	0.65	0.82	0.55	1.00
76	3.25	0.59	0.68	0.58	0.48	0.61	0.72	0.70	0.70	0.80	0.69	0.86	0.83	0.45	0.85	0.51	0.50	0.74	0.74	0.74	0.75	0.53	0.73	0.70	0.85	0.47	0.89	0.57	1.00
77	3.50	0.66	0.63	0.71	0.50	0.73	0.71	0.77	0.77	0.76	0.77	0.75	0.79	0.48	0.82	0.60	0.60	0.80	0.80	0.80	0.79	0.61	0.77	0.66	0.87	0.63	0.91	0.70	1.00
78	3.75	0.76	0.68	0.72	0.49	0.78	0.70	0.80	0.78	0.68	0.82	0.71	0.87	0.58	0.87	0.62	0.66	0.75	0.75	0.83	0.84	0.66	0.88	0.75	0.85	0.74	0.79	0.75	1.00
79	4.00	0.86	0.62	0.84	0.62	0.85	0.86	0.87	0.92	0.79	0.86	0.56	0.82	0.79	0.69	0.84	0.83	0.79	0.79	0.81	0.83	0.83	0.77	0.89	0.76	0.80	0.70	0.83	1.00
80	4.25	0.68	0.63	0.66	0.54	0.65	0.65	0.68	0.75	0.75	0.81	0.65	0.84	0.51	0.71	0.61	0.68	0.83	0.83	0.74	0.77	0.73	0.71	0.82	0.76	0.70	0.64	0.72	1.00
81	4.50	0.81	0.61	0.66	0.54	0.70	0.83	0.74	0.79	0.79	0.72	0.64	0.86	0.75	0.74	0.65	0.82	0.74	0.74	0.73	0.76	0.73	0.74	0.81	0.80	0.69	0.75	0.76	1.00
82	4.75	0.75	0.65	0.64	0.43	0.61	0.77	0.70	0.73	0.77	0.81	0.67	0.88	0.44	0.79	0.65	0.77	0.72	0.72	0.69	0.76	0.67	0.76	0.76	0.78	0.60	0.81	0.71	1.00
83	5.00	0.72	0.72	0.60	0.46	0.63	0.81	0.72	0.76	0.74	0.74	0.70	0.92	0.48	0.79	0.72	0.66	0.73	0.73	0.69	0.72	0.65	0.75	0.82	0.76	0.60	0.72	0.68	1.00
84	5.25	0.69	0.71	0.58	0.48	0.61	0.69	0.70	0.70	0.76	0.75	0.70	0.78	0.40	0.78	0.62	0.61	0.69	0.69	0.62	0.66	0.59	0.75	0.80	0.73	0.59	0.65	0.62	1.00
85	5.50	0.74	0.66	0.70	0.57	0.70	0.83	0.70	0.74	0.74	0.80	0.63	0.79	0.59	0.75	0.57	0.72	0.86	0.86	0.63	0.65	0.60	0.69	0.86	0.73	0.86	0.64	0.67	1.00
86	5.75	0.67	0.76	0.62	0.59	0.71	0.71	0.59	0.68	0.67	0.82	0.71	0.77	0.53	0.74	0.60	0.71	0.74	0.74	0.68	0.65	0.64	0.73	0.85	0.72	0.81	0.67	0.70	1.00
87	6.00	0.82	0.63	0.68	0.61	0.68	0.72	0.68	0.67	0.66	0.73	0.66	0.75	0.57	0.65	0.75	0.69	0.76	0.76	0.63	0.59	0.65	0.65	0.75	0.63	0.66	0.59	0.62	1.00
88	6.25	0.66	0.50	0.75	0.65	0.79	0.68	0.79	0.74	0.54	0.68	0.72	0.61	0.74	0.67	0.70	0.75	0.71	0.71	0.80	0.81	0.64	0.67	0.71	0.56	0.64	0.58	0.77	1.00
89	6.50	0.83	0.64	0.81	0.67	0.80	0.87	0.76	0.79	0.67	0.77	0.84	0.78	0.60	0.77	0.82	0.80	0.84	0.84	0.77	0.74	0.63	0.78	0.81	0.76	0.72	0.81	0.75	1.00
90	6.75	0.72	0.62	0.74	0.88	0.69	0.77	0.72	0.82	0.66	0.85	0.74	0.70	0.64	0.71	0.73	0.88	0.78	0.78	0.78	0.67	0.83	0.76	0.83	0.67	0.74	0.68	0.89	1.00
91	7.00	0.64	0.46	0.70	0.75	0.63	0.63	0.57	0.59	0.50	0.64	0.59	0.52	0.64	0.56	0.63	0.67	0.64	0.64	0.61	0.55	0.73	0.60	0.60	0.56	0.67	0.56	0.69	1.00
92	7.25	0.68	0.52	0.80	0.52	0.69	0.53	0.71	0.54	0.40	0.55	0.49	0.45	0.44	0.54	0.71	0.64	0.55	0.55	0.59	0.68	0.70	0.46	0.59	0.49	0.61	0.53	0.68	1.00
93	7.50	0.59	0.64	0.78	0.64	0.67	0.70	0.60	0.69	0.79	0.78	0.72	0.68	0.54	0.78	0.62	0.71	0.77	0.77	0.66	0.66	0.72	0.68	0.77	0.70	0.68	0.72	0.81	1.00
94	7.75	0.83	0.61	0.75	0.70	0.83	0.82	0.61	0.81	0.64	0.82	0.81	0.66	0.65	0.75	0.79	0.91	0.82	0.82	0.70	0.73	0.81	0.85	0.89	0.77	0.77	0.65	0.82	1.00
95	8.00	0.88	0.61	0.93	0.61	0.88	0.76	0.83	0.88	0.66	0.77	0.79	0.72	0.69	0.64	0.87	0.88	0.88	0.88	0.81	0.67	0.82	0.78	0.86	0.82	0.78	0.62	0.79	1.00
96	8.25	0.82	0.68	0.86	0.76	0.71	0.74	0.76	0.85	0.62	0.94	0.84	0.70	0.52	0.74	0.68	0.87	0.74	0.74	0.85	0.84	0.83	0.82	0.85	0.86	0.74	0.74	0.86	1.00
97	8.50	0.77	0.73	0.84	0.85	0.66	0.76	0.73	0.85	0.77	0.89	0.85	0.78	0.62	0.85	0.82	0.86	0.83	0.83	0.80	0.81	0.87	0.69	0.77	0.76	0.82	0.71	0.76	1.00
98	8.75	0.84	0.79	0.82	0.70	0.79	0.78	0.62	0.80	0.68	0.85	0.79	0.75	0.56	0.83	0.76	0.83	0.77	0.77	0.88	0.80	0.73	0.86	0.79	0.84	0.80	0.75	0.88	1.00
99	9.00	0.83	0.61	0.86	0.82	0.78	0.75	0.84	0.79	0.67	0.77	0.77	0.75	0.67	0.71	0.80	0.94	0.82	0.82	0.78	0.73	0.88	0.66	0.84	0.73	0.77	0.64	0.78	1.00
100	9.25	0.76	0.65	0.72	0.70	0.84	0.81	0.81	0.77	0.67	0.83	0.86	0.78	0.45	0.83	0.87	0.82	0.84	0.84	0.88	0.87	0.77	0.69	0.86	0.78	0.74	0.73	0.88	1.00
101	9.50	0.50	0.73	0.65	0.49	0.69	0.74	0.64	0.71	0.81	0.80	0.78	0.79	0.27	0.90	0.64	0.57	0.69	0.69	0.73	0.82	0.61	0.71	0.73	0.80	0.73	0.81	0.72	1.00
102	9.75	0.60	0.79	0.67	0.54	0.80	0.83	0.77	0.81	0.74	0.85	0.79	0.80	0.42	0.77	0.70	0.69	0.78	0.78	0.79	0.86	0.70	0.78	0.82	0.81	0.77	0.77	0.83	1.00
103	10.00	0.75	0.53	0.67	0.58	0.72	0.78	0.79	0.79	0.66	0.77	0.79	0.66	0.38	0.69	0.58	0.79	0.76	0.76	0.73	0.74	0.79	0.72	0.77	0.69	0.76	0.70	0.78	1.00
104	10.25	0.62	0.74	0.77	0.44	0.77	0.74	0.83	0.81	0.70	0.84	0.86	0.81	0.50	0.79	0.89	0.67	0.83	0.83	0.81	0.85	0.77	0.86	0.86	0.92	0.90	0.75	0.85	1.00
105	10.50	0.84	0.60	0.81	0.59	0.74	0.82	0.84	0.86	0.62	0.86	0.78	0.69	0.72	0.68	0.83	0.78	0.81	0.81	0.71	0.73	0.95	0.88	0.84	0.75	0.70	0.65	0.78	1.00
106	10.75	0.69	0.60	0.77	0.51	0.69	0.66	0.86	0.87	0.68	0.81	0.80	0.75	0.57	0.69	0.67	0.54	0.81	0.81	0.71	0.76	0.81	0.78	0.82	0.79	0.73	0.69	0.86	1.00
107	11.00	0.54	0.79	0.54	0.43	0.64	0.70	0.61	0.66	0.71	0.62	0.68	0.79	0.51	0.76	0.69	0.49	0.71	0.71	0.74	0.73	0.56	0.62	0.72	0.77	0.51	0.67	0.75	1.00
108	11.25	0.71	0.62	0.60	0.51	0.63	0.63	0.59	0.70	0.59	0.64	0.68	0.67	0.54	0.69	0.75	0.69	0.73	0.73	0.57	0.62	0.60	0.80	0.72	0.64	0.53	0.52	0.75	1.00
109	11.50	0.67	0.45	0.63	0.52	0.57	0.77	0.49	0.58	0.58	0.56	0.45	0.69	0.21	0.64	0.69	0.68	0.69	0.69	0.68	0.63	0.57	0.70	0.59	0.64	0.68	0.51	0.66	1.00
110	11.75	0.82	0.43	0.89	0.71	0.67	0.73	0.73	0.76	0.58	0.76	0.58	0.74	0.53	0.74	0.77	0.85	0.79	0.79	0.79	0.75	0.73	0.76	0.81	0.62	0.71	0.77	0.80	1.00
111	12.00	0.66	0.71	0.63	0.55	0.78	0.70	0.66	0.80	0.63	0.70	0.75	0.81	0.45	0.88	0.68	0.63	0.69	0.69	0.73	0.79	0.62	0.78	0.72	0.84	0.61	0.76	0.83	1.00
112	12.25	0.79	0.44	0.80	0.56	0.72	0.69	0.82	0.69	0.51	0.77	0.66	0.57	0.47	0.55	0.72	0.80	0.79	0.79	0.72	0.75	0.78	0.72	0.75	0.59	0.75	0.63	0.79	1.00
113	12.50	0.80	0.57	0.72	0.62	0.80	0.73	0.70	0.73	0.69	0.74	0.70	0.69	0.63	0.62	0.71	0.70	0.84	0.84	0.72	0.79	0.70	0.65	0.79	0.77	0.60	0.72	0.74	1.00
114	12.75	0.59	0.80	0.62	0.48	0.72	0.80	0.54	0.69	0.66	0.64	0.85	0.73	0.46	0.68	0.61	0.52	0.75	0.75	0.70	0.66	0.61	0.69	0.63	0.83	0.73	0.80	0.63	1.00
115	13.00	0.65	0.55	0.67	0.47	0.71	0.51	0.58	0.70	0.59	0.64	0.65	0.79	0.45	0.62	0.64	0.71	0.75	0.75	0.60	0.65	0.64	0.72	0.63	0.76	0.54	0.80	0.68	1.00
116	13.25	0.83	0.49	0.70	0.62	0.91	0.72	0.80	0.79	0.62	0.77	0.57	0.71	0.57	0.76	0.80	0.82	0.92	0.92	0.84	0.69	0.86	0.78	0.46	0.65	0.75	0.79	0.88	1.00
117	13.50	0.60	0.46	0.67	0.55	0.69	0.58	0.59	0.63	0.64	0.64	0.61	0.64	0.67	0.59	0.67	0.62	0.66	0.66	0.61	0.71	0.67	0.59	0.65	0.61	0.71	0.59	0.69	1.00
118	13.75	0.61	0.53	0.70	0.56	0.70	0.73	0.69	0.78	0.65	0.73	0.62	0.66	0.48	0.77	0.78	0.76	0.81	0.81	0.65	0.75	0.75	0.72	0.68	0.71	0.61	0.71	0.74	1.00
119	14.00	0.55	0.56	0.71	0.58	0.73	0.70	0.62	0.70	0.59	0.78	0.62	0.60	0.50	0.71	0.64	0.62	0.69	0.69	0.52	0.73	0.75	0.74	0.60	0.71	0.78	0.64	0.66	1.00
120	14.25	0.49	0.79	0.72	0.48	0.76	0.75	0.62	0.78	0.74	0.70	0.80	0.79	0.69	0.93	0.63	0.73	0.61	0.61	0.61	0.82	0.67	0.79	0.61	0.81	0.77	0.61	0.64	1.00
121	14.50	0.56	0.59	0.61	0.50	0.77	0.71	0.61	0.72	0.76	0.72	0.83	0.81	0.57	0.75	0.69	0.66	0.77	0.77	0.54	0.73	0.64	0.68	0.58	0.88	0.62	0.76	0.74	1.00
122	14.75	0.57	0.83	0.66	0.50	0.78	0.78	0.70	0.00	0.74	0.76	0.82	0.82	0.49	0.85	0.74	0.64	0.89	0.89	0.62	0.81	0.67	0.70	0.72	0.82	0.76	0.84	0.83	1.00
123	15.00	0.67	0.50	0.79	0.68	0.78	0.73	0.78	0.00	0.57	0.63	0.58	0.65	0.50	0.62	0.69	0.85	0.78	0.78	0.71	0.62	0.75	0.70	0.68	0.64	0.81	0.59	0.85	1.00
124	15.25	0.53	0.64	0.77	0.63	0.78	0.73	0.80	0.00	0.65	0.78	0.79	0.80	0.72	0.71	0.72	0.82	0.85	0.85	0.81	0.78	0.77	0.79	0.88	0.84	0.70	0.60	0.81	1.00
125	15.50	0.55	0.56	0.91	0.61	0.82	0.86	0.80	0.00	0.73	0.80	0.67	0.79	0.69	0.78	0.00	0.80	0.87	0.87	0.80	0.81	0.73	0.74	0.74	0.85	0.71	0.67	0.75	1.00
126	15.75	0.57	0.64	0.71	0.66	0.76	0.84	0.74	0.00	0.68	0.85	0.64	0.77	0.58	0.82	0.00	0.75	0.83	0.83	0.75	0.73	0.69	0.82	0.66	0.81	0.71	0.67	0.76	1.00
127	16.00	0.60	0.65	0.72	0.57	0.78	0.83	0.79	0.00	0.69	0.88	0.75	0.86	0.73	0.00	0.00	0.70	0.86	0.86	0.79	0.82	0.71	0.76	0.77	0.81	0.69	0.70	0.76	1.00
128	16.25	0.60	0.54	0.82	0.53	0.83	0.85	0.79	0.00	0.65	0.87	0.82	0.82	0.60	0.00	0.00	0.63	0.85	0.85	0.77	0.85	0.74	0.80	0.71	0.91	0.82	0.75	0.75	1.00
129	16.50	0.60	0.44	0.73	0.64	0.80	0.66	0.73	0.00	0.62	0.88	0.71	0.84	0.67	0.00	0.00	0.75	0.89	0.89	0.77	0.73	0.74	0.00	0.73	0.74	0.66	0.71	0.70	1.00
130	16.75	0.54	0.46	0.70	0.59	0.76	0.59	0.57	0.00	0.65	0.89	0.79	0.69	0.41	0.00	0.00	0.70	0.75	0.75	0.67	0.82	0.74	0.00	0.66	0.84	0.62	0.73	0.71	1.00
131	17.00	0.00	0.40	0.68	0.55	0.69	0.79	0.59	0.00	0.63	0.85	0.82	0.69	0.66	0.00	0.00	0.60	0.60	0.60	0.65	0.91	0.64	0.00	0.62	0.83	0.68	0.60	0.00	1.00
132	17.25	0.00	0.71	0.80	0.62	0.79	0.77	0.87	0.00	0.00	0.84	0.82	0.91	0.00	0.00	0.00	0.73	0.74	0.74	0.82	0.80	0.64	0.00	0.73	0.87	0.80	0.60	0.00	1.00
133	17.50		0.00	0.00	0.00	0.00	0.00	0.00			0.00	0.00	0.00				0.00	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.00		
134	17.75		0.00	0.00	0.00	0.00	0.00	0.00			0.00	0.00	0.00				0.00	0.00	0.00	0.00	0.00				0.00	0.00	0.00		
135	18.00		0.00		0.00	0.00	0.00	0.00				0.00	0.00				0.00	0.00	0.00	0.00	0.00				0.00	0.00	0.00		
136	18.25		0.00			0.00	0.00	0.00					0.00				0.00	0.00	0.00	0.00					0.00	0.00	0.00		
137	18.50		0.00			0.00	0.00	0.00					0.00				0.00	0.00	0.00						0.00	0.00	0.00		
138	18.75		0.00			0.00	0.00	0.00					0.00				0.00	0.00	0.00						0.00	0.00	0.00		
139	19.00		0.00			0.00	0.00	0.00					0.00				0.00	0.00	0.00						0.00	0.00	0.00		

Figure 10: L-CI Map for COSTAR Pre-Trial Benchmark Case 1 Spinal Cord (No Conformity i.e. contour not present (L-CI = 0.00); Poor conformity; Good conformity; Perfect conformity (L-CI = 1.00))

L-CI Map For ART-DECO Pre-Trial Benchmark Case 2 Brainstem

CT Slice No.	Z	PI No.																		Gold Standard
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
16	-11.95																			
17	-11.7																			
18	-11.45																			
19	-11.2									0.00										
20	-10.95									0.00	0.00									
21	-10.7						0.00	0.00	0.00	0.00	0.00	0.00			0.00		0.00	0.00		
22	-10.45	0.00	0.00	0.77	0.00	0.00	0.85	0.74	0.75	0.76	0.77	0.80	0.00	0.00	0.78	0.74	0.89	0.72	0.77	1.00
23	-10.2	0.84	0.00	0.83	0.00	0.00	0.89	0.83	0.86	0.81	0.83	0.81	0.00	0.00	0.86	0.84	0.81	0.86	0.79	1.00
24	-9.95	0.83	0.00	0.85	0.93	0.00	0.87	0.87	0.90	0.88	0.95	0.77	0.00	0.00	0.92	0.83	0.85	0.90	0.84	1.00
25	-9.7	0.77	0.00	0.85	0.87	0.00	0.92	0.87	0.84	0.88	0.91	0.87	0.00	0.00	0.91	0.88	0.85	0.91	0.88	1.00
26	-9.45	0.86	0.00	0.87	0.92	0.89	0.92	0.93	0.82	0.90	0.92	0.87	0.00	0.00	0.90	0.93	0.87	0.91	0.90	1.00
27	-9.2	0.92	0.00	0.80	0.92	0.87	0.92	0.96	0.84	0.89	0.92	0.90	0.86	0.86	0.91	0.91	0.86	0.92	0.93	1.00
28	-8.95	0.88	0.00	0.76	0.90	0.81	0.91	0.93	0.75	0.88	0.91	0.88	0.90	0.90	0.92	0.92	0.87	0.93	0.89	1.00
29	-8.7	0.78	0.00	0.65	0.73	0.65	0.70	0.79	0.78	0.57	0.68	0.79	0.73	0.73	0.74	0.75	0.67	0.76	0.74	1.00
30	-8.45	0.80	0.00	0.64	0.79	0.69	0.89	0.76	0.56	0.71	0.76	0.83	0.81	0.81	0.80	0.83	0.82	0.79	0.74	1.00
31	-8.2	0.81	0.00	0.61	0.79	0.67	0.83	0.66	0.64	0.72	0.66	0.79	0.80	0.80	0.77	0.81	0.79	0.77	0.71	1.00
32	-7.95	0.73	0.00	0.68	0.70	0.71	0.73	0.80	0.60	0.72	0.67	0.64	0.80	0.80	0.72	0.79	0.73	0.64	0.81	1.00
33	-7.7	0.66	0.60	0.75	0.70	0.76	0.82	0.70	0.77	0.81	0.63	0.71	0.74	0.74	0.72	0.86	0.81	0.76	0.74	1.00
34	-7.45	0.74	0.80	0.74	0.62	0.77	0.85	0.85	0.79	0.74	0.65	0.83	0.78	0.78	0.66	0.72	0.64	0.66	0.67	1.00
35	-7.2	0.67	0.69	0.73	0.61	0.68	0.77	0.79	0.83	0.78	0.67	0.73	0.79	0.79	0.65	0.69	0.66	0.64	0.71	1.00
36	-6.95	0.62	0.67	0.64	0.59	0.64	0.67	0.83	0.67	0.64	0.59	0.78	0.81	0.81	0.66	0.68	0.72	0.64	0.68	1.00
37	-6.7	0.80	0.88	0.79	0.66	0.77	0.76	0.72	0.91	0.81	0.68	0.88	0.81	0.81	0.70	0.78	0.69	0.72	0.63	1.00
38	-6.45	0.73	0.79	0.80	0.74	0.80	0.82	0.80	0.78	0.77	0.63	0.85	0.77	0.77	0.78	0.82	0.73	0.79	0.65	1.00
39	-6.2	0.74	0.75	0.66	0.71	0.76	0.80	0.71	0.77	0.74	0.65	0.71	0.66	0.66	0.80	0.79	0.63	0.79	0.70	1.00
40	-5.95	0.64	0.70	0.74	0.70	0.85	0.83	0.79	0.76	0.75	0.71	0.72	0.65	0.65	0.78	0.78	0.64	0.73	0.75	1.00
41	-5.7	0.67	0.79	0.76	0.75	0.78	0.76	0.76	0.78	0.78	0.81	0.84	0.73	0.73	0.73	0.82	0.68	0.68	0.77	1.00
42	-5.45	0.78	0.77	0.77	0.76	0.66	0.82	0.84	0.89	0.86	0.79	0.75	0.86	0.86	0.75	0.85	0.73	0.66	0.75	1.00
43	-5.2	0.71	0.53	0.58	0.00	0.66	0.00	0.76	0.74	0.57	0.62	0.69	0.74	0.74	0.83	0.77	0.80	0.77	0.80	1.00
44	-4.95	0.00	0.00					0.00		0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.00	
45	-4.7							0.00		0.00	0.00		0.00	0.00			0.00	0.00	0.00	
46	-4.45							0.00		0.00								0.00	0.00	
47	-4.2									0.00									0.00	
48	-3.95																		0.00	
49	-3.7																			
50	-3.45																			
51	-3.2																			

Figure 11: L-CI Map for ART-DECO Pre-Trial Benchmark Case 2 Brainstem (No Conformity i.e. contour not present (L-CI = 0.00); Poor conformity; Good conformity; Perfect conformity (L-CI = 1.00))

L-CI Map For ART-DECO Pre-Trial Benchmark Case 1 Left Parotid

CT Slice No.	Z	PI No.																		Gold Standard
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
55	-48.1																			
56	-47.9																			
57	-47.7																			
58	-47.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.58	0.00	0.32	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
59	-47.3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.54	0.00	0.77	0.00	0.00	0.00	0.00	0.00	0.00	0.55	0.49	1.00
60	-47.1	0.00	0.00	0.00	0.00	0.59	0.00	0.00	0.61	0.00	0.76	0.00	0.00	0.00	0.00	0.00	0.74	0.62	0.50	1.00
61	-46.9	0.00	0.00	0.00	0.00	0.37	0.00	0.00	0.45	0.00	0.73	0.00	0.00	0.00	0.00	0.00	0.85	0.48	0.54	1.00
62	-46.7	0.00	0.00	0.00	0.00	0.45	0.49	0.00	0.51	0.00	0.68	0.00	0.00	0.00	0.00	0.00	0.64	0.62	0.56	1.00
63	-46.5	0.00	0.00	0.00	0.00	0.34	0.44	0.00	0.49	0.00	0.79	0.00	0.00	0.00	0.00	0.47	0.69	0.66	0.41	1.00
64	-46.3	0.00	0.00	0.00	0.00	0.67	0.55	0.00	0.65	0.00	0.70	0.30	0.00	0.00	0.00	0.58	0.74	0.65	0.52	1.00
65	-46.1	0.00	0.00	0.00	0.00	0.68	0.57	0.00	0.71	0.00	0.58	0.37	0.00	0.00	0.00	0.52	0.72	0.58	0.43	1.00
66	-45.9	0.00	0.00	0.00	0.00	0.54	0.50	0.00	0.43	0.46	0.55	0.57	0.00	0.00	0.00	0.67	0.44	0.63	0.39	1.00
67	-45.7	0.46	0.49	0.00	0.00	0.65	0.68	0.65	0.47	0.47	0.83	0.55	0.07	0.07	0.42	0.64	0.46	0.71	0.68	1.00
68	-45.5	0.52	0.52	0.00	0.62	0.62	0.65	0.55	0.55	0.49	0.81	0.50	0.58	0.58	0.47	0.72	0.66	0.72	0.58	1.00
69	-45.3	0.67	0.58	0.41	0.70	0.65	0.76	0.55	0.43	0.48	0.78	0.51	0.68	0.68	0.57	0.80	0.68	0.76	0.65	1.00
70	-45.1	0.69	0.57	0.44	0.70	0.71	0.73	0.55	0.29	0.54	0.79	0.57	0.79	0.79	0.64	0.83	0.76	0.83	0.73	1.00
71	-44.9	0.75	0.58	0.38	0.69	0.74	0.79	0.54	0.31	0.78	0.82	0.76	0.75	0.75	0.73	0.78	0.62	0.85	0.66	1.00
72	-44.7	0.74	0.65	0.32	0.72	0.68	0.67	0.48	0.31	0.71	0.74	0.74	0.78	0.78	0.70	0.74	0.59	0.78	0.59	1.00
73	-44.5	0.66	0.84	0.66	0.75	0.77	0.80	0.68	0.71	0.77	0.71	0.76	0.76	0.76	0.81	0.82	0.86	0.83	0.70	1.00
74	-44.3	0.77	0.84	0.57	0.60	0.77	0.79	0.61	0.61	0.81	0.79	0.75	0.79	0.79	0.84	0.80	0.84	0.79	0.77	1.00
75	-44.1	0.76	0.84	0.52	0.62	0.82	0.83	0.60	0.57	0.80	0.77	0.71	0.77	0.77	0.84	0.81	0.79	0.79	0.74	1.00
76	-43.9	0.80	0.83	0.56	0.58	0.80	0.84	0.57	0.60	0.77	0.77	0.77	0.82	0.82	0.81	0.79	0.77	0.80	0.74	1.00
77	-43.7	0.75	0.82	0.52	0.53	0.78	0.74	0.55	0.54	0.75	0.74	0.70	0.85	0.85	0.84	0.74	0.73	0.80	0.68	1.00
78	-43.5	0.83	0.81	0.44	0.52	0.79	0.66	0.49	0.47	0.71	0.81	0.64	0.76	0.76	0.79	0.70	0.68	0.78	0.72	1.00
79	-43.3	0.82	0.87	0.45	0.53	0.83	0.72	0.56	0.52	0.74	0.78	0.66	0.76	0.76	0.80	0.75	0.80	0.79	0.73	1.00
80	-43.1	0.76	0.77	0.48	0.56	0.71	0.70	0.55	0.49	0.70	0.79	0.57	0.75	0.75	0.77	0.70	0.66	0.81	0.73	1.00
81	-42.9	0.80	0.64	0.41	0.51	0.66	0.60	0.63	0.49	0.70	0.83	0.54	0.85	0.85	0.72	0.62	0.64	0.76	0.63	1.00
82	-42.7	0.85	0.60	0.44	0.52	0.74	0.62	0.63	0.42	0.74	0.82	0.66	0.69	0.69	0.77	0.70	0.69	0.79	0.71	1.00
83	-42.5	0.85	0.55	0.39	0.47	0.70	0.63	0.68	0.49	0.70	0.83	0.52	0.47	0.47	0.75	0.70	0.67	0.87	0.79	1.00
84	-42.3	0.71	0.55	0.49	0.54	0.69	0.66	0.58	0.46	0.64	0.64	0.59	0.64	0.64	0.60	0.54	0.44	0.67	0.65	1.00
85	-42.1	0.54	0.48	0.43	0.61	0.71	0.59	0.50	0.45	0.57	0.62	0.51	0.51	0.51	0.50	0.50	0.42	0.65	0.63	1.00
86	-41.9	0.57	0.48	0.52	0.64	0.77	0.62	0.61	0.52	0.59	0.63	0.49	0.58	0.58	0.50	0.56	0.46	0.70	0.64	1.00
87	-41.7	0.60	0.39	0.49	0.56	0.70	0.65	0.56	0.50	0.59	0.70	0.48	0.56	0.56	0.42	0.56	0.53	0.69	0.64	1.00
88	-41.5	0.56	0.00	0.40	0.56	0.59	0.59	0.53	0.50	0.55	0.57	0.51	0.48	0.48	0.34	0.50	0.51	0.58	0.55	1.00
89	-41.3	0.63	0.00	0.60	0.71	0.68	0.68	0.00	0.63	0.74	0.70	0.72	0.68	0.68	0.19	0.75	0.75	0.73	0.62	1.00
90	-41.1	0.69	0.00	0.59	0.64	0.64	0.66	0.00	0.69	0.73	0.68	0.57	0.64	0.64	0.00	0.61	0.78	0.72	0.86	1.00
91	-40.9	0.71	0.00	0.63	0.72	0.54	0.70	0.00	0.62	0.56	0.65	0.73	0.60	0.60	0.00	0.78	0.54	0.67	0.57	1.00
92	-40.7				0.00	0.00	0.00		0.00	0.00	0.00	0.00					0.00	0.00	0.00	
93	-40.5						0.00		0.00		0.00								0.00	
94	-40.3								0.00		0.00									
95	-40.1																			
96	-39.9																			
97	-39.7																			

Figure 12: L-CI Map for ART-DECO Pre-Trial Benchmark Case 1 Left Parotid (No Conformity i.e. contour not present (L-CI = 0.00); Poor conformity; Good conformity; Perfect conformity (L-CI = 1.00))

Chapter 4: Results of Inter-Observer Variation Analysis Between Target Volume, Serial and Parallel OAR Outlines Within Two Lung Cancer Clinical Trials

I collected all the pre-trial benchmark cases for the IDEAL and i-START trials up until November 2012 in DICOM format. In total 198 structures were analysed from both trials based upon three distinct groups – target structures (which included the CTV); serial organs at risk which (included spinal cord and oesophagus) and parallel organs at risk (which included the heart and lungs). The number of structures analysed within each group varied because some submitting clinicians did not include outlines for some of the organs at risk. Details of these grouping are summarised in Table 4 below.

Group Name	Structures Included in Group	Number of Structures Analysed	Total
Target Structures	CTV1	40	40
Serial Organs	Spinal Cord	32	68
	Oesophagus	36	
Parallel Organs	Heart	36	90
	Lungs	54	

Table 4: Summary of IDEAL and i-START Target and OAR Contour Groupings

Descriptive statistics are summarised for the DICE, JACCARD, RIET and 1-GMI indices for each respective group in Table 5. The boxplot as shown in Figure 13 demonstrates that the parallel organs (heart and lungs) had the highest levels of conformality, followed by the target contour (CTV1) and finally the serial organs at risk (oesophagus and spinal cord).

		Number of contours	Mean Index Value	Standard Deviation	95% Confidence Interval for Mean	
					Lower Bound	Upper Bound
DICE	Target	40	0.84	0.10	0.81	0.87
	Serial Organs	68	0.69	0.13	0.65	0.72
	Parallel Organs	90	0.95	0.03	0.95	0.96
	Total	198	0.84	0.15	0.82	0.86
JACCARD	Target	40	0.73	0.13	0.69	0.77
	Serial Organs	68	0.54	0.15	0.50	0.57
	Parallel Organs	90	0.91	0.06	0.90	0.92
	Total	198	0.75	0.20	0.72	0.77
RIET	Target	40	0.72	0.14	0.68	0.77
	Serial Organs	68	0.50	0.16	0.47	0.54
	Parallel Organs	90	0.91	0.06	0.90	0.92
	Total	198	0.73	0.22	0.70	0.76
1-GMI	Target	40	0.86	0.12	0.82	0.90
	Serial Organs	68	0.74	0.19	0.70	0.79
	Parallel Organs	90	0.94	0.05	0.93	0.95
	Total	198	0.86	0.16	0.84	0.88

Table 5: Summary of descriptive statistics for the DICE, JACCARD, RIET and 1-GMI for Target (CTV), Serial Organs (spinal cord and oesophagus) and Parallel Organs (heart and lungs).

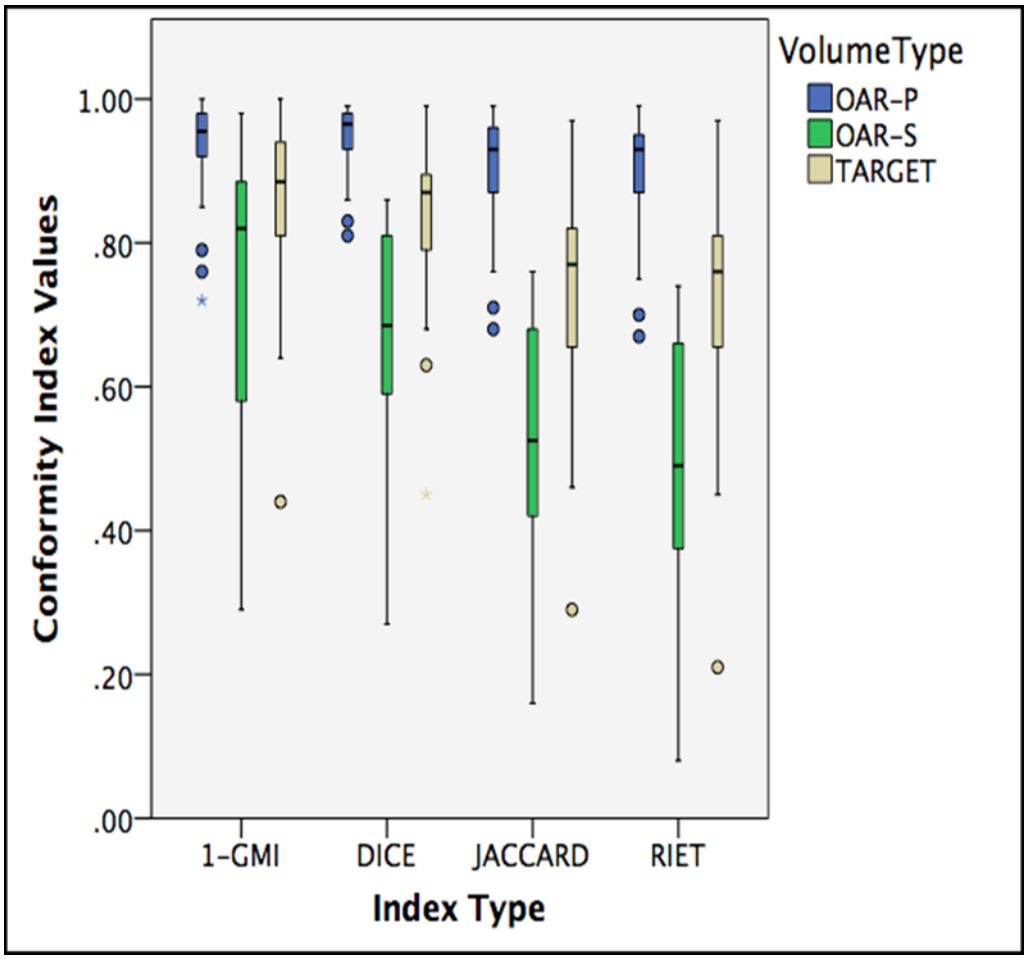


Figure 13: A boxplot displaying the distribution of the DICE, JACCARD, RIET and 1-GMI for OAR-P (heart and lungs), OAR-S (spinal cord and oesophagus) and TARGET (CTV)

A pairwise comparison with Bonferroni correction was performed on each of the groups for each conformity indice (DICE, JACCARD, RIET and 1-GMI). The analysis revealed the following statistical differences between each group and indice analysed:

DICE

A significant difference was found between Target and OAR-S ($p<0.05$)
A significant difference was found between Target and OAR-P ($p<0.05$)
A significant difference was found between OAR-S and OAR-P ($p<0.05$)

JACCARD

A significant difference was found between Target and OAR-S ($p<0.05$)
A significant difference was found between Target and OAR-P ($p<0.05$)
A significant difference was found between OAR-S and OAR-P ($p<0.05$)

RIET

A significant difference was found between Target and OAR-S ($p<0.05$)
A significant difference was found between Target and OAR-P ($p<0.05$)
A significant difference was found between OAR-S and OAR-P ($p<0.05$)

1-GMI

A significant difference was found between Target and OAR-S ($p<0.05$)
A significant difference was found between Target and OAR-P ($p<0.05$)
A significant difference was found between OAR-S and OAR-P ($p<0.05$)

To summarise, a statistically significant difference was detected for the DICE, JACCARD, RIET and 1-GMI indices when target volume contours (TARGET) were

compared with either the serial or parallel organ at risk contours (OAR-S and OAR-P).

A statistically significant difference was also detected for DICE, JACCARD, RIET and 1-GMI indices when the serial and parallel organ at risk contours were compared with each other (OAR-S and OAR-P).

In terms of the individual structures themselves, the boxplot as shown in Figure 14 demonstrates that the lung contours had the highest level of conformity, followed by heart, CTV, spinal cord and oesophagus respectively. Table 6 below summarises the rankings of the organs at risk.

Rank	Structure Name	Group
1st	Lung	OAR-P
2nd	Heart	OAR-P
3rd	CTV1	Target Structure Group
4th	Spinal Cord	OAR-S
5th	Oesophagus	OAR-S

Table 6: Structure and Groups Rankings Based on Conformality Analysis of the IDEAL and i-START Lung Cancer Trials

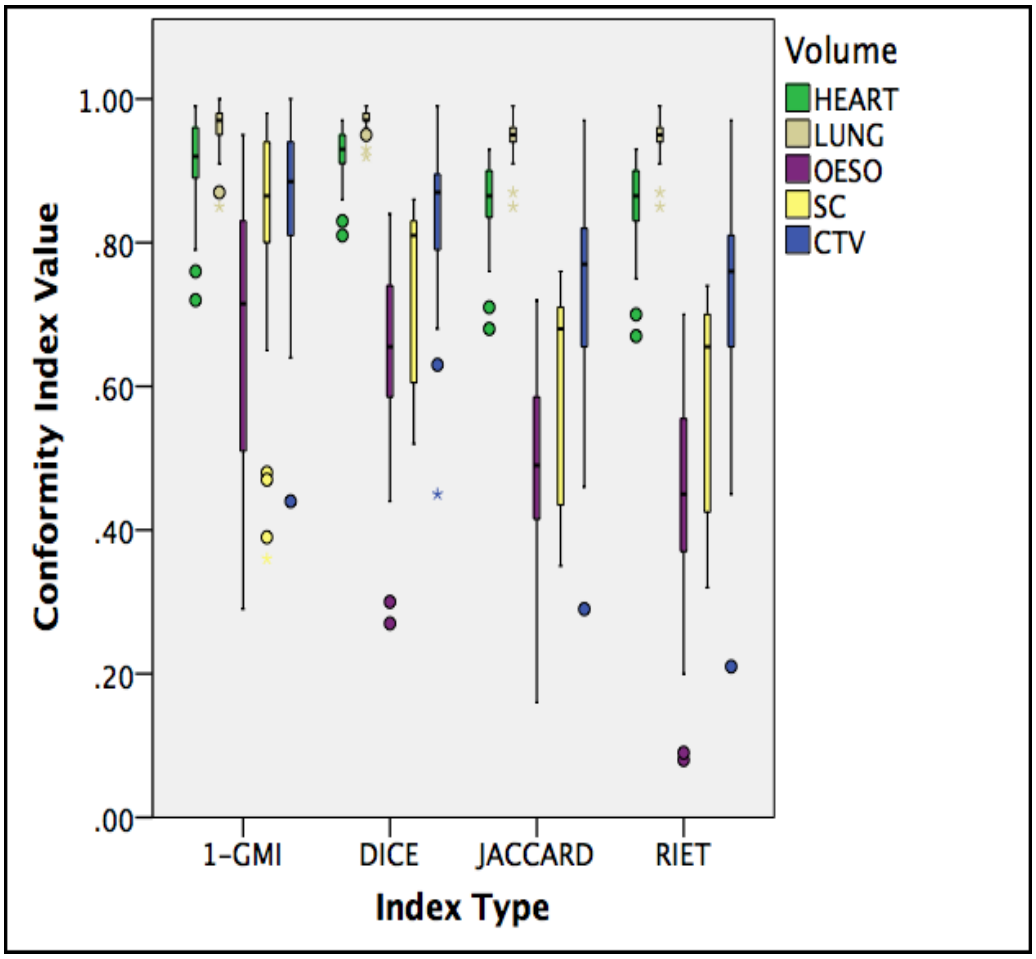


Figure 14: A boxplot displaying the distribution of the DICE, JACCARD, RIET and 1-GMI for individual structures analysed (heart, lung, oesophagus, spinal cord and CTV)

Example L-CI data maps for each of the structures contained within each group analysed can also be seen in Figure 15 – Figure 19. As mentioned in Chapter 3: Results of Inter-Observer Variation Analysis Between Target Volume, Serial and Parallel OAR Outlines Within Two Head and Neck Clinical Trials, the DICE, JACCARD, RIET and 1-GMI indices are single metrics of conformity and therefore condense and obscure the over, under and sometimes subtle differences that can exist between clinician contours. The L-CI data maps for the IDEAL and i-START target volume and OAR structures demonstrate where the highest and lowest levels of conformity exist and clearly reveal those areas of over and under outlining within each submitted target and OAR structure. The L-CI data map allows immediate recognition of where issues may lie and helps to direct the RTQA review to areas in need of greater scrutiny to try and explain why the conformality value seen is lower than expected e.g. misinterpretation of normal CT anatomy or misunderstanding of the radiotherapy contouring protocol.

L-CI Map For IDEAL Pre-Trial Benchmark Case 2 CTV1

CT Slice No.	Z	PI No.												Gold Standard
		1	2	3	4	5	6	7	8	9	10	11	12	
1	-19.20													
2	-18.90													
3	-18.60													
4	-18.30													
5	-18.00													
6	-17.70													
7	-17.40													
8	-17.10													
9	-16.80													
10	-16.50													
11	-16.20													
12	-15.90													
13	-15.60													
14	-15.30													
15	-15.00													
16	-14.70													
17	-14.40													
18	-14.10													
19	-13.80													
20	-13.50													
21	-13.20													
22	-12.90													
23	-12.60							0.00						
24	-12.30							0.00	0.00	0.00	0.00		0.00	
25	-12.00	0.54	0.40	0.64	0.00	0.52	0.00	0.00	0.57	0.62	0.29	0.00	0.27	1.00
26	-11.70	0.85	0.71	0.81	0.62	0.57	0.83	0.00	0.76	0.79	0.44	0.00	0.51	1.00
27	-11.40	0.83	0.76	0.59	0.63	0.54	0.81	0.00	0.76	0.78	0.50	0.68	0.63	1.00
28	-11.10	0.91	0.47	0.40	0.79	0.59	0.82	0.22	0.86	0.90	0.66	0.87	0.84	1.00
29	-10.80	0.78	0.60	0.44	0.72	0.63	0.77	0.35	0.84	0.88	0.71	0.67	0.84	1.00
30	-10.50	0.61	0.66	0.69	0.61	0.73	0.63	0.49	0.59	0.64	0.68	0.45	0.62	1.00
31	-10.20	0.59	0.64	0.83	0.66	0.73	0.66	0.57	0.64	0.64	0.71	0.66	0.58	1.00
32	-9.90	0.55	0.64	0.84	0.60	0.64	0.61	0.64	0.71	0.62	0.66	0.66	0.61	1.00
33	-9.60	0.61	0.76	0.87	0.72	0.61	0.62	0.65	0.79	0.65	0.66	0.64	0.61	1.00
34	-9.30	0.70	0.77	0.91	0.80	0.63	0.68	0.66	0.87	0.69	0.69	0.67	0.65	1.00
35	-9.00	0.72	0.76	0.92	0.84	0.67	0.73	0.66	0.89	0.73	0.74	0.68	0.69	1.00
36	-8.70	0.70	0.79	0.91	0.85	0.73	0.77	0.68	0.87	0.80	0.78	0.71	0.74	1.00
37	-8.40	0.70	0.79	0.92	0.87	0.78	0.80	0.72	0.87	0.83	0.80	0.71	0.78	1.00
38	-8.10	0.69	0.81	0.90	0.86	0.81	0.83	0.76	0.88	0.85	0.79	0.72	0.80	1.00
39	-7.80	0.65	0.80	0.89	0.86	0.82	0.83	0.80	0.85	0.87	0.79	0.76	0.79	1.00
40	-7.50	0.62	0.81	0.89	0.86	0.86	0.83	0.83	0.86	0.89	0.80	0.77	0.79	1.00
41	-7.20	0.65	0.84	0.90	0.87	0.88	0.84	0.85	0.86	0.90	0.83	0.78	0.83	1.00
42	-6.90	0.63	0.82	0.90	0.85	0.88	0.84	0.82	0.86	0.90	0.82	0.73	0.82	1.00
43	-6.60	0.64	0.81	0.88	0.84	0.88	0.84	0.82	0.87	0.90	0.82	0.69	0.82	1.00
44	-6.30	0.67	0.83	0.87	0.83	0.88	0.85	0.84	0.87	0.89	0.83	0.65	0.81	1.00
45	-6.00	0.69	0.86	0.88	0.84	0.87	0.86	0.85	0.88	0.92	0.86	0.68	0.77	1.00
46	-5.70	0.71	0.86	0.87	0.84	0.87	0.88	0.84	0.92	0.94	0.89	0.74	0.78	1.00
47	-5.40	0.72	0.88	0.84	0.82	0.85	0.88	0.82	0.93	0.94	0.89	0.76	0.80	1.00
48	-5.10	0.76	0.89	0.80	0.87	0.84	0.89	0.79	0.88	0.90	0.88	0.77	0.84	1.00
49	-4.80	0.75	0.87	0.85	0.90	0.86	0.91	0.81	0.88	0.89	0.89	0.73	0.85	1.00
50	-4.50	0.75	0.83	0.87	0.86	0.87	0.88	0.81	0.90	0.90	0.86	0.66	0.84	1.00
51	-4.20	0.75	0.84	0.85	0.83	0.91	0.90	0.74	0.90	0.88	0.84	0.64	0.76	1.00
52	-3.90	0.71	0.87	0.78	0.76	0.86	0.88	0.66	0.83	0.78	0.81	0.51	0.62	1.00
53	-3.60	0.68	0.86	0.69	0.65	0.76	0.87	0.63	0.75	0.65	0.77	0.39	0.51	1.00
54	-3.30	0.65	0.81	0.68	0.63	0.63	0.84	0.53	0.64	0.46	0.68	0.24	0.43	1.00
55	-3.00	0.61	0.82	0.71	0.57	0.53	0.80	0.42	0.63	0.34	0.48	0.13	0.27	1.00
56	-2.70	0.63	0.77	0.48	0.31	0.43	0.68	0.47	0.65	0.11	0.32	0.00	0.00	1.00
57	-2.40	0.27	0.66	0.50	0.23	0.00	0.00	0.43	0.60	0.00	0.10	0.00	0.00	1.00
58	-2.10	0.00	0.41	0.42	0.00	0.00	0.00	0.42	0.54	0.00	0.00	0.00	0.00	1.00
59	-1.80		0.00	0.00										
60	-1.50		0.00											
61	-1.20		0.00											
62	-0.90		0.00											
63	-0.60													
64	-0.30													
65	0.00													
66	0.30													
67	0.60													
68	0.90													
69	1.20													
70	1.50													
71	1.80													
72	2.10													
73	2.40													
74	2.70													
75	3.00													
76	3.30													
77	3.60													
78	3.90													
79	4.20													
80	4.50													
81	4.80													
82	5.10													
83	5.40													
84	5.70													
85	6.00													
86	6.30													
87	6.60													
88	6.90													
89	7.20													
90	7.50													
91	7.80													
92	8.10													
93	8.40													
94	8.70													
95	9.00													
96	9.30													
97	9.60													
98	9.90													
99	10.20													
100	10.50													
101	10.80													
102	11.10													
103	11.40													
104	11.70													
105	12.00													

Figure 15: L-CI Map for IDEAL Pre-Trial Benchmark Case 2 CTV1 (No Conformity i.e. contour not present (L-CI = 0.00); Poor conformity; Good conformity; Perfect conformity (L-CI = 1.00))

L-CI Map For IDEAL Pre-Trial Benchmark Case 2 Spinal Cord

CT Slice No.	Z	PI No.												Gold Standard
		1	2	3	4	5	6	7	8	9	10	11	12	
1	-19.20	0.00	0.00	0.00		0.00	0.00		0.00			0.00		
2	-18.90	0.00	0.00	0.00		0.00	0.00		0.00			0.00		
3	-18.60	0.00	0.00	0.00		0.00	0.00		0.00			0.00		
4	-18.30	0.00	0.00	0.00		0.00	0.00		0.00			0.00		
5	-18.00	0.00	0.00	0.00		0.00	0.00		0.00			0.00		
6	-17.70	0.00	0.00	0.00		0.00	0.00	0.00	0.00			0.00		
7	-17.40	0.79	0.71	0.74	0.00	0.81	0.86	0.29	0.72	0.00	0.00	0.82		1.00
8	-17.10	0.81	0.75	0.77	0.00	0.88	0.81	0.25	0.86	0.81	0.00	0.75		1.00
9	-16.80	0.74	0.76	0.85	0.00	0.78	0.83	0.24	0.78	0.71	0.89	0.80		1.00
10	-16.50	0.72	0.80	0.77	0.00	0.83	0.80	0.22	0.73	0.73	0.82	0.80		1.00
11	-16.20	0.71	0.76	0.78	0.00	0.76	0.85	0.22	0.76	0.76	0.81	0.84		1.00
12	-15.90	0.74	0.81	0.86	0.00	0.78	0.88	0.32	0.78	0.77	0.80	0.91		1.00
13	-15.60	0.85	0.80	0.72	0.00	0.73	0.91	0.30	0.75	0.86	0.87	0.88		1.00
14	-15.30	0.76	0.77	0.67	0.00	0.83	0.83	0.38	0.84	0.85	0.83	0.83		1.00
15	-15.00	0.71	0.87	0.68	0.00	0.84	0.77	0.47	0.71	0.87	0.78	0.77		1.00
16	-14.70	0.75	0.88	0.70	0.00	0.85	0.80	0.33	0.74	0.83	0.84	0.83		1.00
17	-14.40	0.77	0.83	0.80	0.75	0.84	0.84	0.33	0.78	0.84	0.83	0.86		1.00
18	-14.10	0.81	0.82	0.85	0.86	0.64	0.89	0.36	0.80	0.87	0.84	0.89		1.00
19	-13.80	0.85	0.85	0.81	0.93	0.87	0.94	0.44	0.74	0.87	0.91	0.92		1.00
20	-13.50	0.85	0.85	0.87	0.93	0.85	0.94	0.35	0.76	0.79	0.87	0.93		1.00
21	-13.20	0.85	0.74	0.85	0.87	0.91	0.87	0.49	0.84	0.71	0.87	0.92		1.00
22	-12.90	0.85	0.87	0.89	0.66	0.70	0.82	0.48	0.87	0.67	0.80	0.91		1.00
23	-12.60	0.85	0.88	0.88	0.72	0.83	0.83	0.51	0.83	0.72	0.89	0.90		1.00
24	-12.30	0.82	0.86	0.82	0.78	0.82	0.86	0.45	0.83	0.80	0.83	0.89		1.00
25	-12.00	0.80	0.73	0.79	0.88	0.80	0.85	0.37	0.76	0.90	0.87	0.90		1.00
26	-11.70	0.86	0.77	0.87	0.86	0.85	0.86	0.42	0.77	0.86	0.78	0.75		1.00
27	-11.40	0.86	0.72	0.82	0.84	0.84	0.80	0.34	0.72	0.81	0.84	0.76		1.00
28	-11.10	0.83	0.73	0.76	0.84	0.83	0.85	0.38	0.71	0.83	0.81	0.89		1.00
29	-10.80	0.80	0.72	0.75	0.76	0.71	0.84	0.41	0.74	0.80	0.79	0.82		1.00
30	-10.50	0.79	0.83	0.84	0.75	0.83	0.89	0.43	0.80	0.84	0.79	0.82		1.00
31	-10.20	0.77	0.66	0.81	0.76	0.80	0.83	0.47	0.75	0.81	0.84	0.88		1.00
32	-9.90	0.74	0.67	0.86	0.76	0.78	0.88	0.55	0.70	0.83	0.85	0.89		1.00
33	-9.60	0.79	0.70	0.82	0.88	0.85	0.88	0.35	0.75	0.87	0.87	0.75		1.00
34	-9.30	0.83	0.75	0.82	0.88	0.85	0.89	0.39	0.71	0.85	0.87	0.79		1.00
35	-9.00	0.85	0.76	0.76	0.91	0.81	0.91	0.39	0.74	0.79	0.87	0.81		1.00
36	-8.70	0.74	0.77	0.79	0.86	0.85	0.79	0.36	0.75	0.77	0.83	0.75		1.00
37	-8.40	0.74	0.70	0.85	0.78	0.85	0.85	0.40	0.74	0.75	0.86	0.77		1.00
38	-8.10	0.72	0.70	0.71	0.72	0.69	0.84	0.46	0.76	0.70	0.86	0.81		1.00
39	-7.80	0.75	0.75	0.82	0.72	0.79	0.86	0.37	0.80	0.73	0.82	0.86		1.00
40	-7.50	0.74	0.84	0.75	0.73	0.85	0.84	0.38	0.76	0.75	0.71	0.82		1.00
41	-7.20	0.74	0.80	0.82	0.84	0.82	0.80	0.40	0.78	0.75	0.67	0.88		1.00
42	-6.90	0.79	0.78	0.88	0.86	0.91	0.83	0.33	0.75	0.68	0.79	0.89		1.00
43	-6.60	0.82	0.71	0.73	0.85	0.85	0.81	0.29	0.71	0.68	0.81	0.88		1.00
44	-6.30	0.81	0.71	0.74	0.83	0.79	0.87	0.31	0.74	0.78	0.68	0.91		1.00
45	-6.00	0.83	0.78	0.84	0.76	0.80	0.88	0.44	0.78	0.71	0.82	0.84		1.00
46	-5.70	0.84	0.86	0.77	0.68	0.81	0.87	0.46	0.78	0.76	0.83	0.85		1.00
47	-5.40	0.83	0.84	0.81	0.72	0.90	0.88	0.43	0.84	0.82	0.85	0.77		1.00
48	-5.10	0.89	0.86	0.76	0.74	0.88	0.90	0.48	0.84	0.82	0.81	0.78		1.00
49	-4.80	0.90	0.83	0.89	0.76	0.89	0.88	0.33	0.83	0.89	0.83	0.76		1.00
50	-4.50	0.87	0.71	0.83	0.88	0.83	0.89	0.35	0.74	0.88	0.78	0.75		1.00
51	-4.20	0.86	0.65	0.74	0.85	0.83	0.88	0.33	0.64	0.85	0.72	0.77		1.00
52	-3.90	0.91	0.71	0.83	0.93	0.89	0.92	0.27	0.72	0.83	0.86	0.82		1.00
53	-3.60	0.88	0.89	0.76	0.94	0.89	0.87	0.33	0.81	0.82	0.89	0.83		1.00
54	-3.30	0.86	0.89	0.81	0.80	0.88	0.87	0.45	0.82	0.79	0.86	0.81		1.00
55	-3.00	0.84	0.80	0.78	0.77	0.83	0.88	0.49	0.82	0.76	0.85	0.80		1.00
56	-2.70	0.80	0.73	0.78	0.70	0.85	0.85	0.48	0.79	0.77	0.84	0.83		1.00
57	-2.40	0.81	0.70	0.82	0.77	0.88	0.89	0.39	0.79	0.84	0.80	0.81		1.00
58	-2.10	0.84	0.69	0.79	0.83	0.87	0.86	0.37	0.77	0.85	0.84	0.83		1.00
59	-1.80	0.84	0.69	0.74	0.89	0.87	0.86	0.39	0.75	0.88	0.84	0.81		1.00
60	-1.50	0.87	0.70	0.69	0.81	0.89	0.92	0.37	0.71	0.87	0.82	0.83		1.00
61	-1.20	0.84	0.76	0.66	0.86	0.91	0.90	0.31	0.64	0.86	0.81	0.82		1.00
62	-0.90	0.82	0.71	0.69	0.92	0.88	0.87	0.37	0.70	0.86	0.80	0.79		1.00
63	-0.60	0.81	0.75	0.80	0.82	0.87	0.85	0.43	0.82	0.82	0.88	0.81		1.00
64	-0.30	0.78	0.74	0.85	0.75	0.84	0.83	0.42	0.83	0.82	0.88	0.79		1.00
65	0.00	0.78	0.62	0.74	0.75	0.81	0.76	0.40	0.78	0.77	0.79	0.78		1.00
66	0.30	0.83	0.51	0.72	0.67	0.87	0.85	0.30	0.77	0.79	0.80	0.65		1.00
67	0.60	0.87	0.65	0.66	0.73	0.92	0.86	0.27	0.67	0.82	0.81	0.65		1.00
68	0.90	0.89	0.72	0.76	0.85	0.90	0.88	0.37	0.73	0.82	0.86	0.84		1.00
69	1.20	0.86	0.71	0.83	0.85	0.94	0.85	0.37	0.71	0.83	0.89	0.84		1.00
70	1.50	0.83	0.60	0.80	0.83	0.89	0.83	0.38	0.71	0.78	0.89	0.79		1.00
71	1.80	0.76	0.71	0.64	0.89	0.82	0.79	0.40	0.78	0.75	0.84	0.78		1.00
72	2.10	0.72	0.73	0.80	0.87	0.81	0.79	0.38	0.84	0.73	0.92	0.76		1.00
73	2.40	0.69	0.68	0.74	0.76	0.79	0.77	0.45	0.80	0.67	0.85	0.77		1.00
74	2.70	0.65	0.48	0.65	0.69	0.72	0.73	0.37	0.75	0.68	0.83	0.64		1.00
75	3.00	0.68	0.39	0.61	0.79	0.74	0.79	0.30	0.73	0.71	0.73	0.67		1.00
76	3.30	0.69	0.39	0.69	0.76	0.73	0.78	0.26	0.77	0.68	0.72	0.66		1.00
77	3.60	0.80	0.33	0.82	0.83	0.80	0.81	0.30	0.63	0.86	0.72	0.81		1.00
78	3.90	0.81	0.71	0.79	0.81	0.85	0.87	0.31	0.63	0.88	0.84	0.81		1.00
79	4.20	0.83	0.73	0.67	0.78	0.89	0.88	0.25	0.68	0.84	0.83	0.83		1.00
80	4.50	0.86	0.73	0.76	0.92	0.92	0.87	0.34	0.71	0.79	0.86	0.87		1.00
81	4.80	0.85	0.65	0.83	0.90	0.88	0.90	0.35	0.79	0.77	0.84	0.88		1.00
82	5.10	0.85	0.87	0.77	0.80	0.84	0.89	0.40	0.81	0.74	0.00	0.93		1.00
83	5.40	0.81	0.79	0.88	0.75	0.80	0.86	0.42	0.76	0.71	0.00	0.84		1.00
84	5.70	0.75	0.77	0.80	0.78	0.83	0.83	0.25	0.75	0.79	0.00	0.76		1.00
85	6.00	0.83	0.78	0.83	0.69	0.74	0.96	0.36	0.74	0.69	0.00	0.76		1.00
86	6.30	0.86	0.79	0.80	0.74	0.84	0.90	0.34	0.65	0.70	0.00	0.77		1.00
87	6.60	0.83	0.60	0.65	0.85	0.85	0.91	0.39	0.78	0.76	0.00	0.73		1.00
88	6.90	0.86	0.77	0.75	0.87	0.87	0.91	0.38	0.79	0.84	0.00	0.88		1.00
89	7.20	0.82	0.81	0.81	0.96	0.82	0.89	0.37	0.81	0.83	0.00	0.86		1.00
90	7.50	0.81	0.85	0.80	0.91	0.88	0.85	0.33	0.83	0.83	0.00	0.78		1.00
91	7.80	0.76	0.61	0.75	0.83	0.86	0.77	0.44	0.74	0.84	0.00	0.69		1.00
92	8.10	0.71	0.73	0.72	0.94	0.82	0.73	0.32	0.83	0.85	0.00	0.66		1.00
93	8.40	0.76	0.68	0.73	0.83	0.85	0.77	0.32	0.77	0.00	0.00	0.68		1.00
94	8.70	0.78	0.62	0.72	0.77	0.78	0.83	0.33	0.81	0.00	0.00	0.69		1.00
95	9.00	0.79	0.61	0.74	0.00	0.76	0.84	0.44	0.78	0.00	0.00	0.73		1.00
96	9.30	0.80	0.62	0.68	0.00	0.77	0.86	0.39	0.74	0.00	0.00	0.73		1.00
97	9.60	0.85	0.54	0.65	0.00	0.76	0.86	0.38	0.74	0.00	0.00	0.71		1.00
98	9.90	0.86	0.56	0.88	0.00	0.77	0.84	0.36	0.71	0.00	0.00	0.79		1.00
99	10.20	0.00	0.60	0.84	0.00	0.79	0.84	0.00	0.79	0.00	0.00	0.76		1.00
100	10.50	0.00	0.58	0.89	0.00	0.78	0.81	0.00	0.77	0.00	0.00	0.76		1.00
101	10.80	0.00	0.76	0.89	0.00	0.84	0.80	0.00	0.81	0.00	0.00	0.83		1.00
102	11.10		0.00	0.00		0.00	0.00		0.00			0.00		
103	11.40		0.00	0.00		0.00	0.00		0.00			0.00		
104	11.70			0.00		0.00	0.00					0.00		
105	12.00			0.00		0.00	0.00					0.00		

Figure 16: L-CI Map for IDEAL Pre-Trial Benchmark Case 2 Spinal Cord (No Conformity i.e. contour not present (L-CI = 0.00); Poor conformity; Good conformity; Perfect conformity (L-CI = 1.00))

L-CI Map For IDEAL Pre-Trial Benchmark Case 1 Oesophagus

CT Slice No.	Z	PI No.												Gold Standard
		1	2	3	4	5	6	7	8	9	10	11	12	
1	-13.80	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
2	-13.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
3	-13.20	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
4	-12.90	0.39	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
5	-12.60	0.28	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
6	-12.30	0.26	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
7	-12.00	0.16	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
8	-11.70	0.39	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.46	1.00
9	-11.40	0.56	0.00	0.00	0.00	0.00	0.00	0.81	0.00	0.00	0.00	0.00	0.70	1.00
10	-11.10	0.69	0.00	0.00	0.00	0.00	0.00	0.86	0.00	0.00	0.00	0.00	0.81	1.00
11	-10.80	0.72	0.86	0.00	0.00	0.00	0.00	0.89	0.00	0.00	0.00	0.00	0.81	1.00
12	-10.50	0.66	0.83	0.00	0.00	0.00	0.00	0.84	0.00	0.00	0.77	0.00	0.88	1.00
13	-10.20	0.70	0.82	0.00	0.00	0.00	0.00	0.85	0.00	0.69	0.77	0.00	0.88	1.00
14	-9.90	0.71	0.78	0.00	0.00	0.00	0.00	0.77	0.00	0.61	0.71	0.00	0.74	1.00
15	-9.60	0.70	0.81	0.00	0.00	0.00	0.00	0.82	0.00	0.54	0.65	0.00	0.78	1.00
16	-9.30	0.66	0.79	0.00	0.00	0.00	0.00	0.86	0.00	0.63	0.70	0.00	0.79	1.00
17	-9.00	0.66	0.85	0.00	0.00	0.00	0.00	0.80	0.00	0.61	0.67	0.00	0.88	1.00
18	-8.70	0.63	0.83	0.15	0.00	0.00	0.67	0.83	0.44	0.66	0.72	0.00	0.87	1.00
19	-8.40	0.57	0.88	0.15	0.00	0.00	0.68	0.88	0.53	0.52	0.69	0.00	0.89	1.00
20	-8.10	0.68	0.86	0.16	0.00	0.00	0.63	0.77	0.48	0.67	0.79	0.00	0.78	1.00
21	-7.80	0.70	0.78	0.17	0.00	0.00	0.63	0.82	0.66	0.78	0.79	0.00	0.79	1.00
22	-7.50	0.85	0.83	0.16	0.00	0.00	0.74	0.84	0.68	0.67	0.87	0.00	0.86	1.00
23	-7.20	0.76	0.72	0.18	0.00	0.00	0.70	0.82	0.57	0.75	0.79	0.00	0.72	1.00
24	-6.90	0.77	0.82	0.27	0.00	0.00	0.70	0.73	0.57	0.76	0.79	0.00	0.78	1.00
25	-6.60	0.78	0.82	0.45	0.00	0.00	0.82	0.70	0.44	0.75	0.79	0.00	0.84	1.00
26	-6.30	0.74	0.80	0.50	0.00	0.00	0.63	0.69	0.45	0.59	0.78	0.00	0.76	1.00
27	-6.00	0.71	0.71	0.54	0.00	0.00	0.55	0.77	0.49	0.68	0.68	0.00	0.81	1.00
28	-5.70	0.71	0.72	0.48	0.78	0.78	0.58	0.69	0.34	0.59	0.72	0.00	0.65	1.00
29	-5.40	0.73	0.78	0.48	0.79	0.79	0.65	0.75	0.42	0.71	0.77	0.00	0.85	1.00
30	-5.10	0.70	0.78	0.36	0.77	0.77	0.58	0.67	0.57	0.67	0.72	0.72	0.77	1.00
31	-4.80	0.74	0.79	0.46	0.75	0.75	0.76	0.77	0.43	0.71	0.74	0.73	0.82	1.00
32	-4.50	0.68	0.78	0.58	0.73	0.73	0.72	0.86	0.62	0.76	0.80	0.84	0.85	1.00
33	-4.20	0.70	0.78	0.57	0.69	0.69	0.67	0.79	0.52	0.80	0.75	0.79	0.87	1.00
34	-3.90	0.77	0.76	0.58	0.76	0.76	0.69	0.73	0.59	0.75	0.76	0.83	0.80	1.00
35	-3.60	0.69	0.81	0.61	0.87	0.87	0.68	0.78	0.48	0.74	0.77	0.84	0.89	1.00
36	-3.30	0.54	0.85	0.58	0.73	0.73	0.78	0.84	0.69	0.77	0.92	0.76	0.67	1.00
37	-3.00	0.60	0.82	0.63	0.67	0.67	0.72	0.85	0.58	0.81	0.87	0.88	0.81	1.00
38	-2.70	0.68	0.79	0.71	0.68	0.68	0.71	0.78	0.60	0.75	0.77	0.83	0.83	1.00
39	-2.40	0.83	0.88	0.58	0.73	0.73	0.69	0.86	0.64	0.63	0.76	0.72	0.84	1.00
40	-2.10	0.79	0.74	0.64	0.71	0.71	0.77	0.88	0.66	0.56	0.82	0.81	0.86	1.00
41	-1.80	0.82	0.73	0.68	0.73	0.73	0.62	0.87	0.74	0.68	0.78	0.82	0.84	1.00
42	-1.50	0.81	0.68	0.67	0.74	0.74	0.82	0.81	0.81	0.78	0.76	0.79	0.85	1.00
43	-1.20	0.75	0.66	0.59	0.59	0.59	0.85	0.90	0.89	0.86	0.82	0.74	0.82	1.00
44	-0.90	0.60	0.59	0.60	0.78	0.78	0.74	0.85	0.69	0.80	0.82	0.71	0.84	1.00
45	-0.60	0.54	0.65	0.38	0.76	0.76	0.71	0.82	0.58	0.76	0.82	0.72	0.79	1.00
46	-0.30	0.40	0.57	0.18	0.63	0.63	0.88	0.80	0.74	0.64	0.75	0.72	0.71	1.00
47	0.00	0.33	0.40	0.06	0.40	0.40	0.46	0.64	0.23	0.42	0.52	0.64	0.21	1.00
48	0.30	0.35	0.54	0.29	0.30	0.30	0.50	0.74	0.49	0.51	0.56	0.70	0.39	1.00
49	0.60	0.61	0.76	0.47	0.44	0.44	0.66	0.65	0.42	0.82	0.63	0.66	0.78	1.00
50	0.90	0.65	0.70	0.64	0.52	0.52	0.75	0.75	0.57	0.75	0.69	0.79	0.77	1.00
51	1.20	0.64	0.70	0.51	0.49	0.49	0.74	0.80	0.46	0.77	0.75	0.73	0.76	1.00
52	1.50	0.71	0.57	0.58	0.59	0.59	0.77	0.74	0.48	0.62	0.57	0.60	0.70	1.00
53	1.80	0.68	0.57	0.56	0.60	0.60	0.69	0.72	0.37	0.54	0.50	0.54	0.75	1.00
54	2.10	0.68	0.55	0.46	0.51	0.51	0.59	0.73	0.44	0.53	0.64	0.67	0.68	1.00
55	2.40	0.75	0.57	0.44	0.47	0.47	0.66	0.65	0.40	0.53	0.73	0.54	0.89	1.00
56	2.70	0.71	0.51	0.34	0.41	0.41	0.75	0.64	0.47	0.56	0.76	0.55	0.78	1.00
57	3.00	0.63	0.45	0.15	0.38	0.38	0.80	0.70	0.61	0.50	0.77	0.43	0.78	1.00
58	3.30	0.73	0.50	0.28	0.49	0.49	0.71	0.71	0.64	0.51	0.73	0.08	0.70	1.00
59	3.60	0.80	0.46	0.38	0.50	0.50	0.66	0.68	0.86	0.53	0.64	0.38	0.73	1.00
60	3.90	0.73	0.51	0.54	0.45	0.45	0.68	0.63	0.64	0.53	0.54	0.65	0.81	1.00
61	4.20	0.64	0.58	0.57	0.39	0.39	0.69	0.51	0.66	0.51	0.46	0.46	0.71	1.00
62	4.50	0.61	0.63	0.69	0.46	0.46	0.70	0.59	0.56	0.63	0.59	0.63	0.67	1.00
63	4.80	0.48	0.64	0.44	0.65	0.65	0.72	0.68	0.58	0.54	0.58	0.54	0.63	1.00
64	5.10	0.61	0.49	0.35	0.49	0.49	0.29	0.52	0.46	0.40	0.44	0.48	0.67	1.00
65	5.40	0.67	0.67	0.49	0.59	0.59	0.70	0.71	0.80	0.60	0.64	0.68	0.71	1.00
66	5.70	0.54	0.67	0.51	0.50	0.50	0.68	0.68	0.62	0.64	0.70	0.83	0.62	1.00
67	6.00	0.51	0.68	0.48	0.44	0.44	0.60	0.63	0.79	0.51	0.68	0.74	0.74	1.00
68	6.30	0.70	0.70	0.54	0.57	0.57	0.80	0.89	0.75	0.56	0.87	0.72	0.79	1.00
69	6.60	0.76	0.68	0.62	0.53	0.53	0.70	0.83	0.65	0.57	0.72	0.76	0.67	1.00
70	6.90	0.69	0.68	0.71	0.48	0.48	0.80	0.77	0.77	0.66	0.73	0.80	0.78	1.00
71	7.20	0.71	0.77	0.63	0.50	0.50	0.75	0.85	0.69	0.67	0.76	0.80	0.80	1.00
72	7.50	0.74	0.71	0.64	0.56	0.56	0.66	0.76	0.62	0.57	0.68	0.71	0.67	1.00
73	7.80	0.81	0.77	0.53	0.63	0.63	0.45	0.74	0.63	0.51	0.59	0.24	0.63	1.00
74	8.10	0.85	0.82	0.54	0.61	0.61	0.61	0.78	0.57	0.57	0.66	0.42	0.64	1.00
75	8.40	0.69	0.72	0.47	0.66	0.66	0.59	0.85	0.49	0.54	0.47	0.31	0.72	1.00
76	8.70	0.70	0.73	0.44	0.70	0.70	0.64	0.83	0.50	0.58	0.47	0.20	0.59	1.00
77	9.00	0.68	0.81	0.53	0.63	0.63	0.81	0.84	0.59	0.64	0.41	0.40	0.65	1.00
78	9.30	0.71	0.83	0.58	0.83	0.83	0.54	0.79	0.71	0.53	0.56	0.43	0.73	1.00
79	9.60	0.65	0.75	0.70	0.81	0.81	0.71	0.87	0.79	0.56	0.74	0.58	0.78	1.00
80	9.90	0.66	0.71	0.72	0.72	0.72	0.71	0.84	0.66	0.59	0.68	0.28	0.63	1.00
81	10.20	0.76	0.79	0.61	0.84	0.84	0.78	0.81	0.45	0.55	0.61	0.48	0.68	1.00
82	10.50	0.71	0.80	0.60	0.80	0.80	0.69	0.82	0.54	0.52	0.59	0.45	0.67	1.00
83	10.80	0.61	0.77	0.54	0.63	0.63	0.77	0.76	0.59	0.46	0.57	0.41	0.79	1.00
84	11.10	0.00		0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
85	11.40	0.00		0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00		
86	11.70	0.00			0.00	0.00	0.00		0.00	0.00	0.00	0.00		
87	12.00	0.00					0.00		0.00	0.00	0.00	0.00		
88	12.30	0.00							0.00		0.00	0.00		
89	12.60	0.00										0.00		
90	12.90													

Figure 17: L-CI Map for IDEAL Pre-Trial Benchmark Case 1 Oesophagus (No Conformity i.e. contour not present (L-CI = 0.00); Poor conformity; Good conformity; Perfect conformity (L-CI = 1.00))

L-CI Map For IDEAL Pre-Trial Benchmark Case 1 Heart

CT Slice No.	Z	PI No.												Gold Standard
		1	2	3	4	5	6	7	8	9	10	11	12	
1	-13.80													
2	-13.50													
3	-13.20													
4	-12.90													
5	-12.60													
6	-12.30													
7	-12.00													
8	-11.70													
9	-11.40													
10	-11.10													
11	-10.80													
12	-10.50													
13	-10.20													
14	-9.90													
15	-9.60													
16	-9.30													
17	-9.00													
18	-8.70													
19	-8.40													
20	-8.10													
21	-7.80													
22	-7.50													
23	-7.20													
24	-6.90													
25	-6.60													
26	-6.30													
27	-6.00													
28	-5.70													
29	-5.40													
30	-5.10													
31	-4.80													
32	-4.50													
33	-4.20													
34	-3.90													
35	-3.60													
36	-3.30													
37	-3.00													
38	-2.70													
39	-2.40													
40	-2.10													
41	-1.80													
42	-1.50													
43	-1.20													
44	-0.90													
45	-0.60													
46	-0.30			0.00										
47	0.00			0.00										
48	0.30			0.00										
49	0.60			0.00										
50	0.90			0.00										
51	1.20			0.00										
52	1.50			0.00										
53	1.80			0.00										
54	2.10			0.00										
55	2.40	0.00		0.00			0.00		0.00					
56	2.70	0.80	0.87	0.80	0.00	0.00	0.91	0.00	0.88	0.91	0.00	0.00	0.95	1.00
57	3.00	0.81	0.89	0.81	0.86	0.86	0.95	0.92	0.90	0.93	0.00	0.00	0.94	1.00
58	3.30	0.87	0.92	0.89	0.90	0.90	0.93	0.93	0.90	0.95	0.00	0.88	0.94	1.00
59	3.60	0.86	0.88	0.92	0.93	0.93	0.94	0.94	0.92	0.94	0.00	0.89	0.94	1.00
60	3.90	0.87	0.87	0.93	0.91	0.91	0.94	0.93	0.90	0.95	0.00	0.88	0.93	1.00
61	4.20	0.93	0.90	0.91	0.88	0.88	0.95	0.95	0.90	0.95	0.00	0.90	0.92	1.00
62	4.50	0.92	0.83	0.93	0.93	0.93	0.95	0.93	0.88	0.92	0.00	0.91	0.90	1.00
63	4.80	0.91	0.89	0.91	0.89	0.89	0.92	0.94	0.90	0.94	0.00	0.90	0.89	1.00
64	5.10	0.89	0.88	0.93	0.91	0.91	0.96	0.93	0.92	0.92	0.95	0.92	0.89	1.00
65	5.40	0.88	0.87	0.94	0.90	0.90	0.95	0.94	0.92	0.92	0.94	0.93	0.89	1.00
66	5.70	0.88	0.88	0.94	0.91	0.91	0.95	0.93	0.92	0.95	0.94	0.95	0.94	1.00
67	6.00	0.90	0.88	0.95	0.93	0.93	0.96	0.95	0.94	0.96	0.94	0.95	0.95	1.00
68	6.30	0.88	0.88	0.96	0.94	0.94	0.97	0.94	0.93	0.94	0.94	0.94	0.95	1.00
69	6.60	0.84	0.86	0.95	0.90	0.90	0.94	0.92	0.91	0.90	0.94	0.91	0.93	1.00
70	6.90	0.86	0.87	0.94	0.95	0.95	0.96	0.94	0.92	0.91	0.95	0.91	0.94	1.00
71	7.20	0.87	0.86	0.94	0.93	0.93	0.95	0.94	0.89	0.90	0.94	0.91	0.93	1.00
72	7.50	0.90	0.88	0.94	0.94	0.94	0.95	0.93	0.94	0.92	0.94	0.92	0.95	1.00
73	7.80	0.93	0.92	0.92	0.96	0.96	0.96	0.95	0.92	0.94	0.94	0.91	0.96	1.00
74	8.10	0.92	0.93	0.92	0.95	0.95	0.97	0.94	0.94	0.94	0.94	0.92	0.97	1.00
75	8.40	0.92	0.93	0.93	0.94	0.94	0.96	0.95	0.92	0.96	0.94	0.94	0.96	1.00
76	8.70	0.92	0.92	0.94	0.97	0.97	0.96	0.93	0.90	0.96	0.93	0.93	0.96	1.00
77	9.00	0.92	0.91	0.93	0.95	0.95	0.96	0.91	0.88	0.96	0.94	0.94	0.97	1.00
78	9.30	0.92	0.92	0.90	0.94	0.94	0.96	0.92	0.91	0.97	0.94	0.94	0.98	1.00
79	9.60	0.91	0.93	0.94	0.95	0.95	0.97	0.92	0.88	0.96	0.95	0.95	0.96	1.00
80	9.90	0.93	0.95	0.94	0.94	0.94	0.96	0.93	0.87	0.94	0.95	0.96	0.93	1.00
81	10.20	0.92	0.94	0.91	0.93	0.93	0.94	0.94	0.83	0.93	0.93	0.93	0.91	1.00
82	10.50	0.93	0.92	0.89	0.91	0.91	0.91	0.92	0.86	0.93	0.91	0.92	0.91	1.00
83	10.80	0.91	0.90	0.87	0.89	0.89	0.92	0.91	0.88	0.82	0.91	0.90	0.95	1.00
84	11.10	0.92	0.90	0.84	0.87	0.87	0.94	0.92	0.87	0.84	0.90	0.88	0.92	1.00
85	11.40	0.89	0.90	0.89	0.89	0.89	0.91	0.94	0.79	0.75	0.87	0.89	0.90	1.00
86	11.70	0.90	0.91	0.92	0.94	0.94	0.91	0.92	0.82	0.61	0.85	0.92	0.93	1.00
87	12.00	0.89	0.88	0.89	0.83	0.83	0.87	0.90	0.85	0.60	0.80	0.85	0.92	1.00
88	12.30	0.91	0.89	0.90	0.77	0.77	0.86	0.88	0.62	0.61	0.71	0.82	0.91	1.00
89	12.60	0.86	0.71	0.77	0.80	0.80	0.79	0.85	0.50	0.69	0.81	0.63	0.89	1.00
90	12.90	0.64	0.77	0.00	0.53	0.53	0.77	0.85	0.00	0.26	0.51	0.67	0.52	1.00

Figure 18: L-CI Map for IDEAL Pre-Trial Benchmark Case 1 Heart (No Conformity i.e. contour not present (L-CI = 0.00); Poor conformity; Good conformity; Perfect conformity (L-CI = 1.00))

L-CI Map For i-START Pre-Trial Benchmark Case 1 Left Lung

CT Slice No.	Z	PI No.									Gold Standard
		1	2	3	4	5	6	7	8	9	
1	-13.80										
2	-13.50										
3	-13.20										
4	-12.90										
5	-12.60										
6	-12.30										
7	-12.00										
8	-11.70										
9	-11.40										
10	-11.10										
11	-10.80										
12	-10.50										
13	-10.20										
14	-9.90										
15	-9.60										
16	-9.30										
17	-9.00										
18	-8.70					0.72	0.86	1.00		0.59	1.00
19	-8.40					0.82	0.95	1.00		0.81	1.00
20	-8.10					0.90	0.94	1.00		0.89	1.00
21	-7.80					0.85	0.95	1.00		0.91	1.00
22	-7.50					0.91	0.96	1.00		0.90	1.00
23	-7.20					0.94	0.96	1.00		0.94	1.00
24	-6.90					0.91	0.97	1.00		0.94	1.00
25	-6.60					0.96	0.97	1.00		0.95	1.00
26	-6.30					0.96	0.97	0.99		0.95	1.00
27	-6.00					0.97	0.97	0.99		0.95	1.00
28	-5.70					0.95	0.97	1.00		0.96	1.00
29	-5.40					0.98	0.97	1.00		0.95	1.00
30	-5.10					0.98	0.98	1.00		0.96	1.00
31	-4.80					0.96	0.97	0.99		0.95	1.00
32	-4.50					0.97	0.97	0.99		0.96	1.00
33	-4.20					0.97	0.97	0.99		0.96	1.00
34	-3.90					0.96	0.97	0.99		0.97	1.00
35	-3.60					0.93	0.98	1.00		0.97	1.00
36	-3.30					0.96	0.97	0.99		0.97	1.00
37	-3.00					0.96	0.97	0.98		0.97	1.00
38	-2.70					0.96	0.97	0.97		0.96	1.00
39	-2.40					0.98	0.97	0.99		0.97	1.00
40	-2.10					0.98	0.97	0.99		0.96	1.00
41	-1.80					0.98	0.97	0.99		0.96	1.00
42	-1.50					0.98	0.97	0.99		0.97	1.00
43	-1.20					0.97	0.96	0.99		0.97	1.00
44	-0.90					0.98	0.97	0.99		0.96	1.00
45	-0.60					0.98	0.97	0.99		0.97	1.00
46	-0.30					0.97	0.97	0.99		0.96	1.00
47	0.00					0.98	0.97	0.99		0.95	1.00
48	0.30					0.96	0.97	0.99		0.97	1.00
49	0.60					0.98	0.97	0.99		0.97	1.00
50	0.90					0.96	0.97	0.99		0.97	1.00
51	1.20					0.96	0.97	0.96		0.95	1.00
52	1.50					0.95	0.92	0.97		0.92	1.00
53	1.80					0.90	0.95	0.97		0.92	1.00
54	2.10					0.95	0.94	0.99		0.93	1.00
55	2.40					0.97	0.95	0.99		0.93	1.00
56	2.70					0.93	0.96	0.98		0.93	1.00
57	3.00					0.97	0.97	0.98		0.94	1.00
58	3.30					0.96	0.97	0.98		0.94	1.00
59	3.60					0.95	0.97	0.98		0.95	1.00
60	3.90					0.96	0.95	0.99		0.94	1.00
61	4.20					0.95	0.96	0.99		0.94	1.00
62	4.50					0.95	0.97	0.99		0.95	1.00
63	4.80					0.92	0.95	0.99		0.93	1.00
64	5.10					0.93	0.95	0.98		0.95	1.00
65	5.40					0.93	0.95	0.98		0.95	1.00
66	5.70					0.93	0.95	0.98		0.95	1.00
67	6.00					0.93	0.95	0.98		0.95	1.00
68	6.30					0.94	0.96	0.98		0.95	1.00
69	6.60					0.93	0.95	0.98		0.95	1.00
70	6.90					0.93	0.95	0.98		0.94	1.00
71	7.20					0.94	0.96	0.98		0.94	1.00
72	7.50					0.94	0.96	0.98		0.94	1.00
73	7.80					0.93	0.95	0.98		0.94	1.00
74	8.10					0.92	0.95	0.98		0.94	1.00
75	8.40					0.93	0.95	0.98		0.94	1.00
76	8.70					0.93	0.96	0.98		0.94	1.00
77	9.00					0.93	0.95	0.98		0.95	1.00
78	9.30					0.94	0.95	0.99		0.96	1.00
79	9.60					0.94	0.96	0.99		0.96	1.00
80	9.90					0.94	0.96	0.99		0.96	1.00
81	10.20					0.93	0.96	0.99		0.96	1.00
82	10.50					0.93	0.96	0.99		0.95	1.00
83	10.80					0.94	0.97	0.99		0.94	1.00
84	11.10					0.95	0.97	0.99		0.92	1.00
85	11.40					0.93	0.84	0.99		0.60	1.00
86	11.70					0.76	0.92	0.97		0.73	1.00
87	12.00					0.70	0.84	0.91		0.69	1.00
88	12.30					0.69	0.84	0.79		0.68	1.00
89	12.60					0.67	0.83	0.62		0.62	1.00
90	12.90					0.75	0.65	0.56		0.46	1.00

Figure 19: L-CI Map for i-START Pre-Trial Benchmark Case 1 Left Lung (No Conformity i.e. contour not present (L-CI = 0.00); Poor conformity; Good conformity; Perfect conformity (L-CI = 1.00))

Chapter 5: Results of The Head and Neck Pre-Trial Benchmark Case Resubmission Analysis.

For both the ART-DECO and COSTAR head and neck trials, if the respective RTQA team conducting the benchmark case review judged the submitted contours to be non-compliant with the trial protocol then constructive feedback was generated in the form of an analysis report and sent to the submitting clinician. The clinician was requested to re-submit their updated contours using the feedback contained within the analysis report.

I collected all the pre-trial benchmark case resubmissions for both the ART-DECO and COSTAR trials up until June 2012 in DICOM format. Again, the structures analysed were grouped together using the same distinct groupings as in chapter 3 – target structures (which included the high dose CTV); serial organs at risk (spinal cord and brainstem) and parallel organs at risk (parotid gland). Details of these grouping are again summarised in Table 7 below.

Group Name	Structures Included in Group	Number of Structures Analysed	Total
Target Structures (TARGET)	CTV1 (high dose CTV)	63	63
Serial Organs (OAR-S)	Spinal Cord	63	126
	Brainstem	63	
Parallel Organs (OAR-P)	Left Parotid	63	99
	Right Parotid	36	

Table 7: Summary of COSTAR and ARTDECO Target and OAR Contour Groupings

All resubmission contours were analysed for DICE, JACCARD, RIET and 1-GMI indices and then compared against their initial submission using the Wilcoxon signed rank test to determine whether any statistically significant difference existed. Descriptive statistics are summarised for the DICE, JACCARD, RIET and 1-GMI indices for each

respective group for both first and final submissions in Table 8. The table also includes the mean percentage difference for paired submissions for all the indices analysed following contour resubmissions. This was determined by first calculating the percentage difference between an individual clinicians first submission contour CI value and their final submission contour CI value. The mean was then calculated for the whole group and this process was repeated for every structure and CI analysed. The results are displayed in the final column of Table 8 and demonstrate that there was a positive mean improvement in all four measured conformality indices. There was variation though between the three groups in the magnitude of the improvement seen. Overall the serial organs seemed to have the highest mean percentage difference improvement. It should be noted though that the confidence intervals for the serial organ Dice, Van't Riet and 1-GMI indices did include negative percentage values. This would suggest that for some of the re-submitted contours analysed following RTQA feedback, the submitting clinician had incorrectly re-edited their contours prior to resubmitting them.

The boxplots shown in Figure 20 to Figure 23 illustrate the distribution of the four conformity indices between the first and final submission for the Target, OAR-S and OAR-P groups. Analysis of the head and neck pre-trial benchmark case resubmission data revealed a statistically significant improvement in all measured conformity indices (DICE, JACCARD RIET and GMI) for all three groups (TARGET, OAR-S and OAR-P) following RTQA feedback.

As explained in Appendix 1, modification of the layout of the L-CI grid (substituting each PI column with re-submissions by the same PI), made it possible to visually demonstrate the changes made to a structure over the course of re-submissions. Hence, Figure 24 clearly demonstrates how the CTV1, left parotid, right parotid, brainstem and spinal cord volumes for a single clinician were improved following RTQA feedback over the course of 3 submissions during the ART-DECO pre-trial benchmark case period.

The L-CI data map helps to identify precisely where adaptations were needed following the initial submission and subsequently made following the 2 – 3 subsequent re-submissions following RTTQA review and feedback.

Conformity Index	Types of Contour	First Submission Mean Index Value (95%CI)	Final Submission Mean Index Value (95%CI)	P Value	Mean Percentage Difference for Paired Submissions (95%CI)
DICE	Target	0.80 (0.78-0.82)	0.83 (0.82-0.85)	P<0.05	5.8% (1.7%-9.8%)
	OAR-S	0.73 (0.71-0.76)	0.77 (0.75-0.78)	P<0.05	11.3% (-1.2%-23.8%)
	OAR-P	0.74 (0.72-0.76)	0.77 (0.75-0.78)	P<0.05	4.4% (2.7%-7.2%)
JACCARD	Target	0.67 (0.64-0.69)	0.74 (0.72-0.76)	P<0.05	12.9% (5.8%-20.0%)
	OAR-S	0.59 (0.57-0.62)	0.66 (0.64-0.68)	P<0.05	27.0% (5.7%-48.4%)
	OAR-P	0.59 (0.57-0.61)	0.64 (0.62-0.66)	P<0.05	9.7% (6.0%-13.4%)
RIET	Target	0.65 (0.62-0.67)	0.71 (0.69-0.73)	P<0.05	13.9% (4.7%-23.1%)
	OAR-S	0.57 (0.54-0.59)	0.61 (0.59-0.63)	P<0.05	38.6% (-12.1%-89.3%)
	OAR-P	0.56 (0.54-0.59)	0.60 (0.58-0.62)	P<0.05	7.9% (4.85-11.0%)
1-GMI	Target	0.78 (0.74-0.81)	0.82 (0.80-0.85)	P<0.05	10.0% (0.3%-19.8%)
	OAR-S	0.77 (0.74-0.80)	0.82 (0.79-0.84)	P<0.05	20.8% (-3.6%-45.1%)
	OAR-P	0.71 (0.69-0.74)	0.75 (0.73-0.77)	P<0.05	6.8% (3.6%-9.9%)

Table 8: Descriptive statistics for DICE, JACCARD. RIET and 1-GMI indice analysis of 1st and final submissions for Target, OAR-S and OAR-P Contours

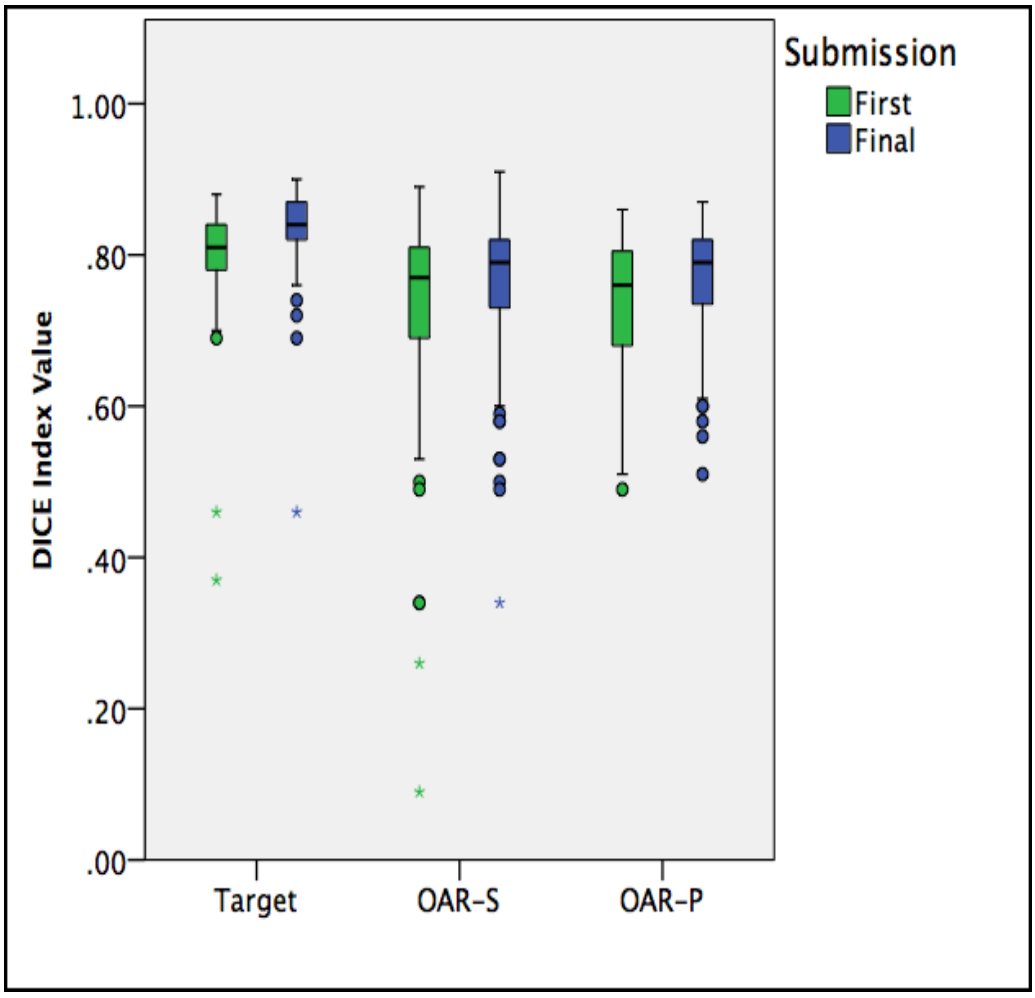


Figure 20: Analysis of 1st and final submission DICE indice for Target, OAR-S and OAR-P Contours

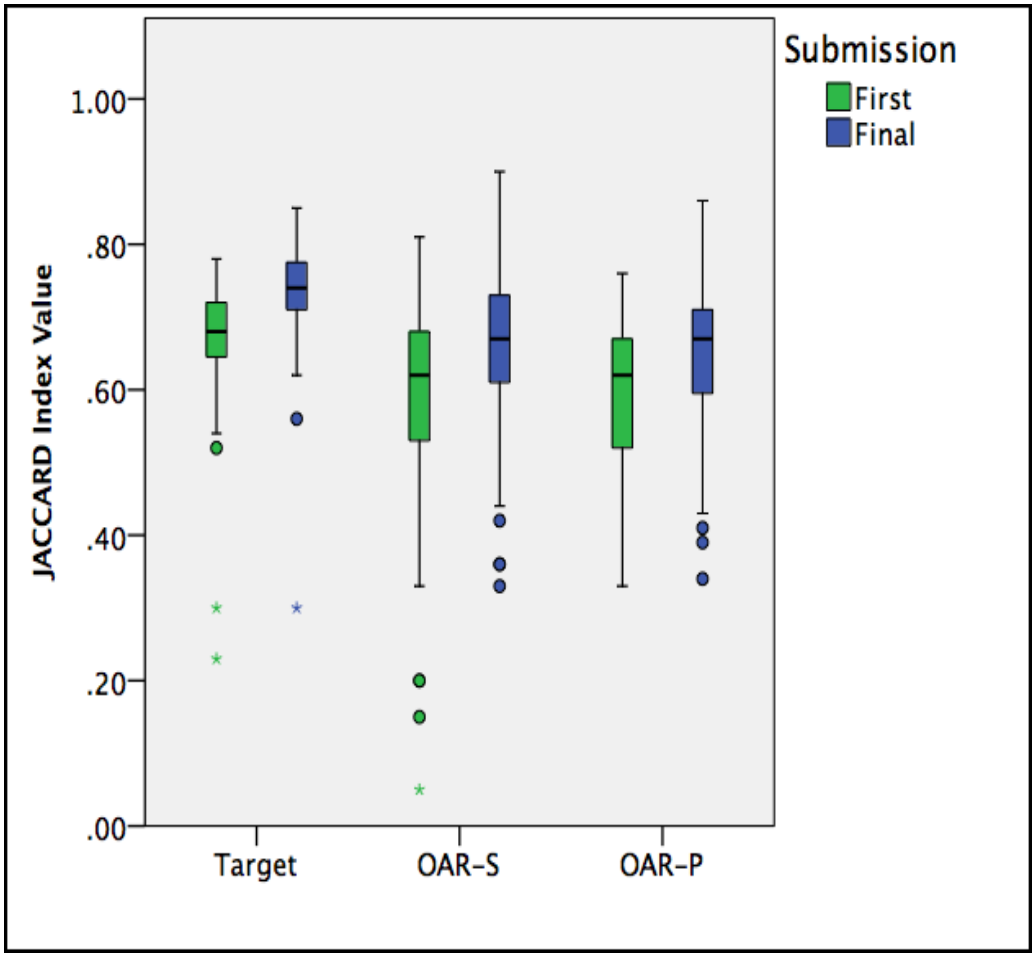


Figure 21: Analysis of 1st and final submission JACCARD indice for Target, OAR-S and OAR-P Contours

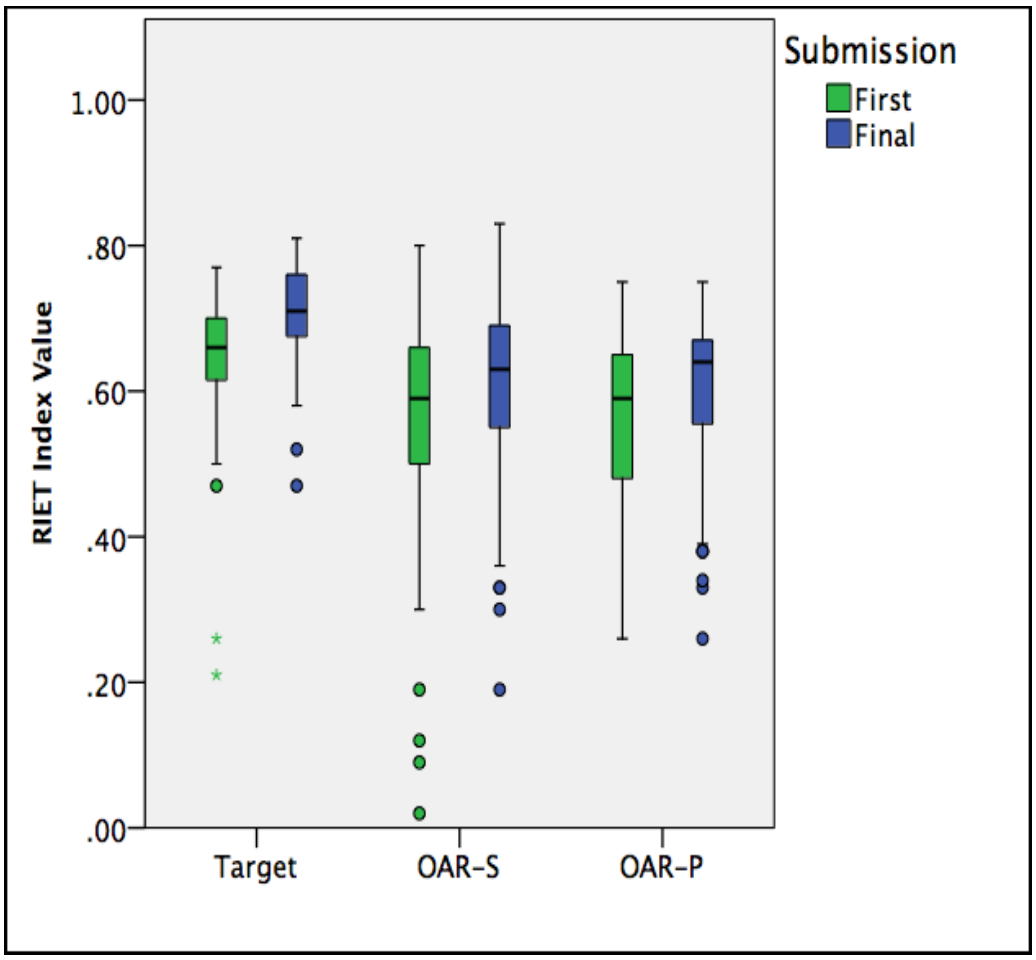


Figure 22: Analysis of 1st and final submission RIET indice for Target, OAR-S and OAR-P Contours

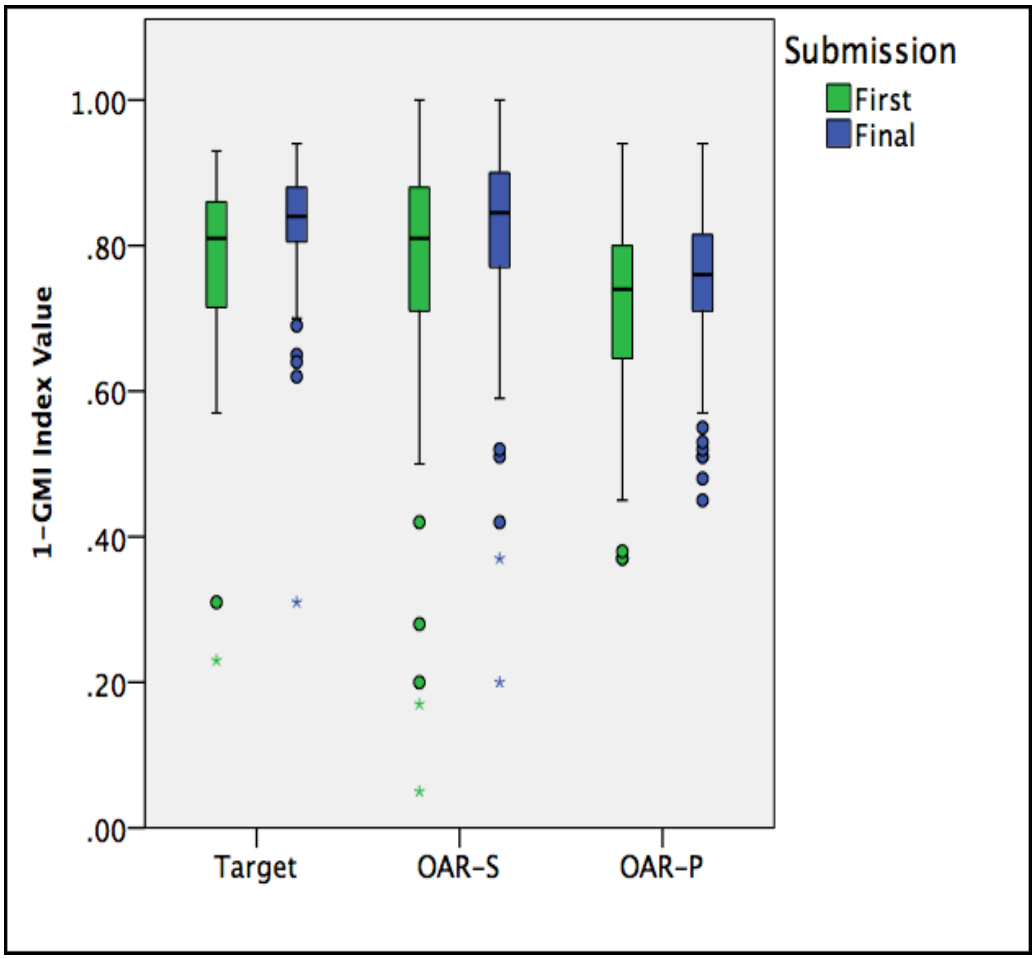


Figure 23: Analysis of 1st and final submission 1-GMI indice for Target, OAR-S and OAR-P Contours

Impact of RTQA Feedback on Clinician Contouring Demonstrated Using L-CI Data

Figure 24: Impact of RTQA Feedback on an Individual Clinician Contouring Demonstrated Using L-CI Data During The ART-DECO Trial (No Conformity i.e. contour not present (L-CI = 0.00); Poor conformity; Good conformity; Perfect conformity (L-CI = 1.00))

Chapter 6: Discussion

Head and Neck Pre-Trial Benchmark Cases

Analysis of the ART-DECO and COSTAR pre-trial benchmark case target volumes, serial organs (OAR-S) and parallel organs (OAR-P) volumes has revealed that a statistically significant difference does exist between clinician target and organ at risk volumes. Therefore, the hypothesis that there is a significant level of inter-observer variation amongst clinical oncologist's target volume and OAR contours within the context of the pre-trial quality assurance (QA) benchmark cases for two different UK head and neck radiotherapy trials can be accepted.

Table 3 summarises the descriptive statistics for all four indices analysed and reveals relatively high levels of conformity for both the Dice and 1-GMI conformity indices (indice range 0.71 – 0.80) for the target structure and parallel and serial organs at risk volumes. The Jaccard Index and Van't Riet indices for all three groups were lower though with values ranging between 0.56 and 0.67.

The Jaccard Conformity Index is the ratio of intersection of two volumes, as compared with the union of the two volumes under comparison. The Dice co-efficient and Van't Riet indice are mathematically similar to the Jaccard Index but also assess for variations in under and over outlining respectively.

The results reveal that all three groups had high levels of conformity when analysed using the Dice co-efficient (range 0.73 – 0.80). Slightly lower levels of conformity were seen when measured using the Jaccard Conformity Index (range 0.59 – 0.67) and Van't Riet indice (range 0.56 – 0.65). My analysis suggests low levels of under-outlining based upon both the Dice co-efficient and 1-GMI results (the 1-GMI results ranged between 0.71 – 0.78). For all four indices, the highest levels of conformality were seen in the target group with lower, albeit similar levels of conformality, in the serial and parallel organ at risk groups.

Comparison of the three groups also revealed that there were statistical differences between the target group and the serial and parallel organ at risk groups for the Dice, Jaccard and Van't Riet indices ($p<0.05$). These results suggest that clinician target outlining within the benchmark cases is more consistent than organ at risk outlining. This could be explained on the basis that the target volume contains the tumour (or an area at risk of harbouring residual tumour cells post-surgery) and is therefore deemed by the clinician to be the most important volume to be defined because sub-optimal definition negatively impacts on the chances of cure. Hence it is therefore likely to be the volume defined most accurately by the treating clinician.

This concept might also explain why the target group had such low levels of under outlining when assessed using the Dice co-efficient (mean value 0.80) and 1-GMI indices (mean value 0.78). When defining the target volume i.e. the GTV or CTV, clinicians will always try to avoid missing out macroscopic tumour or areas considered to be at-risk of harbouring microscopic disease from their volume. Hence, it would seem more likely that clinicians will tend to over outline rather than under outline their target volume. Assessment of the Van't Riet index for the target group was lower than that of the Dice co-efficient (mean value 0.65) and would seem to support this.

It should be noted that target volume definition (CTV1) within both the ART-DECO and COSTAR trial outlining protocols was comprehensively covered. Participating clinicians were instructed to define their target volumes (CTV1) using normal anatomical boundaries and their respective landmarks. This is likely to have reduced inter-observer variation as anatomical landmarks tend to be well defined and easy to locate in head and neck normal tissue CT and MRI atlases. Both the trials' respective radiotherapy planning packs also contained nodal atlases, guidance on which nodal levels to include in the high dose volume (CTV1) and comprehensive example cases with example contours defined on example CT data sets. This level of information is likely to have reduced inter-observer variability and led to the improved conformality detected through my analysis of the target contours.

Conversely, the radiotherapy planning packs for both the trials contained much less information to aid clinician contouring of organs at risk structures. In the case of the parotid glands (parallel organ at risk group), brainstem and spinal cord (serial organ at risk group), clinicians were instructed to outline them with little or no information on their normal anatomical boundaries or an atlas to visually aid their definition. Consequently, this might help to explain why the organ at risk values were lower than those seen for the target volume group.

Analysis of the serial and parallel contour groups did not reveal any statistically significant differences for the DICE, Jaccard or Van't Riet indices. This would suggest that both groups were contoured equally well by the submitting clinicians although as already discussed, not as well as the target group. There was a statistically significant difference detected in the 1-GMI results for the serial and parallel organ groups. Review of Table 3 also reveals that the parallel organs had higher levels of under outlining when compared to the serial organ group. This might be explained on the basis that the true extent of the parallel organs (parotid glands) are more difficult to accurately define than the serial organs (spinal cord and brainstem) and that the radiotherapy planning packs contained relatively less information to aid their delineation than compared to the target volume group.

The UK SCOPE I trial revealed a Jaccard Conformity Index (JCI) for investigator GTV's of 0.69 which they found was comparable with JCI values published in three different studies (JCI values 0.69 – 0.72) [57, 61-63]. The mean JCI value for the ART-DECO and COSTAR trial target volume group was 0.67 (CI 0.64 – 0.69) which would seem consistent with those previously published. Hence, target volume conformality within the ART-DECO and COSTAR trials would seem to be consistent with that seen in the UK SCOPE I trial and other published studies [57, 61-63].

Lung Pre-Trial Benchmark Cases

Analysis of the IDEAL and i-START pre-trial benchmark case target volumes, serial organs (OAR-S) and parallel organs (OAR-P) volumes has revealed that a statistically significant difference does exist between clinician target and organ at risk volumes. Therefore, the hypothesis that there is a significant level of inter-observer variation amongst clinical oncologist's target volume and OAR contours within the context of the pre-trial quality assurance (QA) benchmark cases for two different UK lung radiotherapy trials can be accepted.

Table 5 summarises the descriptive statistics for all four indices analysed and reveals high levels of conformity for the Dice, Jaccard, Van't Riet and 1-GMI conformity indices for the target structure and the parallel organ at risk groups (indice range 0.72 – 0.95). The serial organ at risk group though had relatively lower values for all four measured indices with the lowest being the Van't Riet (mean value 0.50), then the Jaccard Index (mean value 0.54) followed by the Dice co-efficient (mean value 0.69) and finally the highest being the 1-GMI indice (mean value 0.74).

My results would suggest low levels of both under and over outlining in the target and parallel organ at risk groups based upon the results of the DICE co-efficient, Van't Riet and 1-GMI indices. For the target structure group (CTV1), the mean indice values for DICE, Van't Riet and 1-GMI were 0.84 (CI 0.81 – 0.87), 0.72 (CI 0.68 – 0.77) and 0.86 (CI 0.82 – 0.90) respectively. For the parallel organs at risk group (heart and lungs) the mean indice values for DICE, Van't Riet and 1-GMI were 0.95 (CI 0.95 – 0.96), 0.91 (CI 0.90 – 0.92) and 0.94 (CI 0.93 – 0.95) respectively. For the serial organs at risk group (spinal cord and oesophagus), my results would suggest higher levels of under-outlining based on the mean 1-GMI (0.74; CI 0.70 – 0.79) and Dice (0.69; CI 0.65 – 0.72) results. Based on the Van't Riet results seen in the serial organs at risk group (mean 0.50; CI 0.47 – 0.54), over outlining also seemed to be an issue in this group.

A study of Figure 14 which displays the distribution of conformity indices for each individual structure analysed reveals some unexpected results. Unlike in the UK head and neck radiotherapy trial data where CTV1 (Target Structure Group) had the highest overall mean conformity index values, in the UK lung radiotherapy trial benchmark case data, CTV1 was ranked 3rd overall in the group with the remaining structures ordered as shown in Table 6.

This ranking would suggest that in the context of the IDEAL and i-START trials, the lung volumes had the highest levels of conformity whilst the oesophagus had the lowest. Compared with the head and neck rankings (Figure 8), this is very different because CTV1 ranked first overall (Target Structures), the spinal cord and brainstem (OAR-S) second, and the parotid glands (OAR-P) third.

In the head and neck trial data discussion it was postulated that the target volumes are the ones most likely to have the highest conformity values because they contain the tumour target (or an area considered at high risk of containing microscopic disease) and therefore are the ones clinicians are likely to outline most accurately. It is therefore interesting to see in the lung trial data analysis that the target volume comes third, below the parallel organ at risk contours (lung and heart respectively).

In the head and neck trials, target volumes (CTV1) were defined using comprehensive outlining guidelines which referenced anatomical boundaries and anatomical landmarks to help guide head and neck clinicians contouring. In the IDEAL and i-START trials though, the radiotherapy outlining protocols did not contain such detailed guidance because typically in lung cancer, the CTV is normally a geometric expansion of the GTV edited off normal structure boundaries. Therefore, the CTV1 volume in lung cancer contouring can be at greater risk of inter-observer variation as it is ultimately defined by the underlying GTV volume which is essentially delineated by the treating lung clinician using all available diagnostic imaging and the clinician's own interpretation of the CT planning scan. The process of defining the GTV volume relies heavily on the delineating clinician's own ability to interpret the diagnostic imaging findings and the boundaries of normal and abnormal anatomy on the patient's radiotherapy planning scan.

Thus, based on my findings, it would seem there is greater uncertainty and therefore more likelihood of inter-observer variation during lung cancer target volume delineation. Consequently, this might explain why in the IDEAL and i-START structure analysis, the CTV1 structure came 3rd in the rankings of structures based on the outcome of the conformality analysis (Table 6).

What is also interesting from the structure rankings is that the lung contours, which are normally auto-contoured using the auto-segmentation function of the treatment planning system and therefore not normally outlined by the treating clinician, are first in the rankings. These findings would seem to validate the ability of the auto-segmentation software to accurately outline lungs based on the high levels of conformality seen for the submitted lung contours when compared against the TMGs reference contours.

The other unexpected finding based on Figure 14, is that the heart outline came second amongst the structure rankings. This again conflicts with the concept that serial organs are easier to outline than parallel ones based on the idea that serial organs are tubular in shape, whereas parallel organs typically have more varied geometrical borders. What also highlights this unexpected finding further is that the lowest ranked structures (4^{th} and 5^{th}) were the spinal cord and oesophagus respectively. Both these structures are considered serial organs and anatomically are normally long tubular structures. These findings would seem to cast doubt on the idea that serial structures are easier to outline than parallel ones based on their geometric properties and would suggest that certainly in the case of the oesophagus, based on its anatomical location and proximity to other central mediastinal structures, it is difficult to interpret its precise boundaries and anatomical course.

Analysis of the three groups revealed that there were statistically significant differences between the target group and the serial and parallel OAR groups for all four indices analysed ($p<0.05$). The results of the analysis would seem to validate the differences seen in the mean indices for Dice, Jaccard Index, Van't Riet and 1-GMI for target and organ at risk contours detailed in the discussion above.

The mean JCI value for the IDEAL and i-START trial target volume group was 0.73 (CI 0.69 – 0.77) and seems consistent with the published UK SCOPE I trial target volume JCI of 0.69. Hence, target volume conformality within the IDEAL and i-START trials seems to be consistent with that seen in the UK SCOPE I trial.

Impact of RTQA Feedback on Head and Neck Pre-Trial Benchmark Case Resubmissions

Analysis of the head and neck pre-trial benchmark case resubmission data found statistically significant differences between the first and the final target, OAR-P and OAR-S contours submitted for RTQA assessment ($p<0.05$). In fact, the target, OAR-P and OAR-S structures analysed from the ART-DECO and COSTAR benchmark cases showed statistically significant improvements in all 4 conformity indices analysed ($p<0.05$). Based on this, the hypothesis that RTQA feedback during the pre-trial benchmark period does positively influence head and neck clinician contouring can be accepted.

Analysis of the resubmitted head and neck benchmark cases using L-CI data maps has also helped to demonstrate how a clinician's contours evolve over the course of RTQA feedback and subsequent re-submissions. Figure 24 clearly demonstrates how one clinician's contours evolved over the course of a total of 3 submissions. For instance, on the first submission, Figure 24 reveals that the clinician's CTV1 and brainstem contours had low levels of conformity on CT slices 87 – 100 and 53 – 66 respectively. Following RTQA feedback and subsequent resubmission, column 2 now reveals improved conformality for both structures compared with the TMG reference contours (shown in column 4). Using the L-CI data map shown in Figure 24, it would seem the submitting clinician re-contoured CT slices 91 – 104 and 55 – 74 of their CTV1 and brainstem respectively. They also removed two erroneous slices of their brainstem contour (CT slices 79 and 80) and inspection of their spinal cord contour reveals these were added correctly to this structure instead to improve the junction point between the brainstem and spinal cord structures. Inspection of the third submission L-CI data map (column 3) suggests no further amendments were made to their CTV1 contour but they did add new contours on CT slices 53 – 54 for their brainstem (although the conformality of these contours was lower compared with others contained within the structure (LCI values 0.42 and 0.46 respectively)).

Overall, Figure 24 demonstrates the value of the L-CI data maps in helping to highlight areas of high and low contouring conformity over the full extent of a clinicians delineated target volume or OAR structure. The L-CI data map allows immediate recognition of where issues may lie and helps to direct attention to where greater scrutiny is needed to try to explain why conformality is lower than expected e.g. misinterpretation of normal anatomy or misunderstanding of the radiotherapy protocol.

The L-CI is also capable of revealing precisely how RTQA feedback, following RTQA review, can influence clinician contouring on a CT slice by slice basis following subsequent resubmissions. Through this enhanced level of detail, the L-CI helps to explain why there was a statistically significant improvement in all 4 conformity indices analysed for the head and neck structures which underwent RTQA review and subsequent feedback during the ART-DECO and COSTAR pre-trial benchmark period. The L-CI is therefore a valuable tool which complements other conformity indices (i.e. Dice, Jaccard, Van't Riet and GMI) because unlike those other indices, which are effectively 1-dimensional due to their single integer assessment of clinician conformality, the L-CI can display a 2-dimensional map of conformity and thus can display a more nuanced level of detail.

Chapter 7: Conclusions

Analysis of the pre-trial benchmark cases from UK head and neck and lung cancer trials has yielded a wealth of data highlighting the degree of inter-observer variability that exists in contouring in UK radiotherapy trials. The results of the analysis have revealed that most of the target volumes and OAR contours analysed from the pre-trial benchmark cases met published standards (JCI values ≥ 0.69) [83, 87-89]. It was also revealed that target volumes are not always the ones to have the highest levels of contouring conformity. Variation in the levels of target volume and OAR contouring conformity was found to exist between the head and neck and lung cancer trials and raised important questions why these differences might exist.

Based on the head and neck pre-trial benchmark cases, it seems that more information within the radiotherapy outlining protocol relating to target volume contouring combined with an anatomical approach to target volume boundaries helps to improve target volume conformality amongst clinicians. Conversely, it would also seem that a lack of detail defining the anatomical boundaries of organs at risk also results in lower levels of clinician conformity. Thus, it would seem vitally important that to ensure adequate conformity amongst clinicians that the radiotherapy trial outlining protocol contains detailed information on how target volume and organ at risk volumes should be defined with example cases and/or CT atlases for clinician use.

Analysis of the lung cancer pre-trial benchmark cases has also revealed unexpected findings regarding the rankings of the target and organ at risk contours based on their respective conformity indice values. My results found the target volume to be in the middle of the rankings with the parallel organ at risk volumes at the top and the serial organ at risk volumes at the bottom. This seems surprising as I would have hypothesised that the volume containing the tumour target would have a higher level of conformity than the organ at risk volumes on the basis that they are the most critical ones for achieving a potential cure.

However, based on the results this was not the case and instead the highest ranked structure was the lung contours which are typically automatically outlined by the treatment planning software rather than a human being. These results though do seem to validate the ability of radiotherapy treatment planning software to auto-contour normal lung volumes with a very high degree of conformality (range 0.91 – 0.95 for the four indices analysed). Therefore, I suspect that as radiotherapy treatment planning software continues to advance that its ability to auto-contour other normal organs might also develop with hopefully the same high level of conformality it can currently achieve when delineating the normal lungs.

The analysis of the lung cancer benchmark cases has again also highlighted the importance of including detailed and systematic instructions on the outlining of target and normal structures. Given the relatively low conformality indice values for the spinal cord and oesophagus contours it seems imperative that future radiotherapy trial outlining protocols include clear definitions and systematic instructions on how to outline normal organs at risk. The inclusion of an atlas should also be considered so to demonstrate more clearly how the normal organ should be defined on a CT slice by slice basis. These measures lead to improved conformality amongst participating clinicians as demonstrated by the results of the head and neck pre-trial benchmark case analysis where the radiotherapy outlining protocol did include some of these measures.

This research has also demonstrated the value of the local conformity index (L-CI) in helping to pinpoint quickly and easily the precise area(s) within contoured structures where the highest levels of inter-observer variability exist (Figure 9 – Figure 12, Figure 15 – Figure 19 and Figure 24 help demonstrate this). As opposed to the Dice, Jaccard, Van't Riet and GMI indices, the L-CI allows the reviewer's attention to be quickly directed to those underperforming areas within the delineated structure to help try and explain why conformality is lower than expected e.g. misinterpretation of normal anatomy or misunderstanding of the radiotherapy protocol. The Dice, Jaccard, Van't Riet and GMI indices on the other hand essentially provide a summary of the structures conformity with the added benefit of information on under or over outlining depending on the indice used. The

L-CI however offers itself as a broader tool than those more traditional conformity indices as it can be used during the RTQA review process to provide more detailed feedback on structure outlining e.g. feedback on a CT slice by slice basis.

However, the process of creating the L-CI is more intensive and time consuming than compared with analysing the traditional Dice, Jaccard, Van't Riet and GMI indices and should therefore only really be considered when such a level of detail is truly needed e.g. adding a deeper layer of information to help explain why a measured traditional indice might be lower than one might expect. Thus, the L-CI complements the traditional indices which are themselves able to provide a more rapid, one dimensional assessment of contouring conformity.

By combining the pre-trial benchmark cases with the L-CI it also allows the radiotherapy trial management group to dynamically monitor, and if necessary, review and update the radiotherapy outlining protocol to overcome potential shortcomings. For instance, if analysis of the pre-trial benchmark cases using the L-CI were to reveal unexpectedly low levels of conformality for an organ at risk or target structure then it could help prompt a review of the radiotherapy outlining protocol to determine whether more can be done to reduce inter-observer variability. This could involve improved guidance on how the structure should be delineated, the inclusion of an example case or a CT atlas demonstrating how the structure is outlined or perhaps a TMG organised contouring workshop for participating clinicians.

Analysis of the resubmitted ART-DECO and COSTAR pre-trial benchmark cases has also revealed that radiotherapy quality assurance feedback during the pre-accrual benchmark period can improve clinician conformity. This was demonstrated by a statistically significant improvement in the mean Dice, Jaccard, Riet and 1-GMI indices for all target and OAR structures analysed following resubmission.

The L-CI data maps were also shown to be invaluable during to RTQA feedback process in helping to demonstrate visually on a CT slice by slice basis how individual clinician contours evolve over the course of RTQA feedback and subsequent

resubmissions. This important finding validates the benefits of radiotherapy quality assurance, particularly during the pre-accrual benchmark period.

Chapter 8: Future Work

This work has analysed the degree of interobserver variation in the context of UK head and neck and lung cancer trials. Work has also already been published on the analysis of the UK SCOPE 1 pre-trial benchmark cases which studied inter-observer variation in the delineation of oesophageal cancer target volumes [64]. As pre-trial benchmark cases are becoming more integrated into UK radiotherapy trials future work could include the analysis of said cases in the context of other tumour sites such as cervical, bladder, lymphoma and the recent stereotactic radiotherapy studies which cover multiple sites within the body. Analysis of these other tumour sites could help to determine where the greatest levels of inter-observer variation exits in the context of target and organ at risk outlining and help evolve existing and future radiotherapy outlining protocols to help reduce inter-observer variability and improve target and organ at risk contouring amongst participating clinicians.

Both the IDEAL and i-START lung cancer radiotherapy trials shared the same pre-trial benchmark cases, but both had different TMG reference contours for their target and organ at risk contours. In future it would be useful to conduct a comparative analysis of these two TMG reference contours sets to determine the degree of inter-observer variation that can exist between two 'expert groups'. This analysis could lead to some interesting results and subsequent discussion on the role of alternative methods for the creation of reference contour sets which can influence the degree of inter-observer variability detected during contour conformity analysis.

The Radiation Therapy Oncology Group (RTOG) has utilised the 'simultaneous truth and performance level estimation' (STAPLE) algorithm to create single reference contour sets for its atlases. This technique utilises the STAPLE algorithm to create a single contour set from multiple different expert contours [66-69]. Recently this method was used to create the reference contour set for the UK's INTERLACE trial which is evaluating the potential benefits of chemotherapy prior to chemoradiation for cervical cancer. This method of combining expert opinions to create a reference contour set has already been shown by the SCOPE1 team to statistically improve

the number of submitting trial clinicians judged as achieving an excellent conformity level by 53% [70]. This approach should therefore be seriously considered by future TMG groups when defining their reference contours.

One key element this work has not evaluated is the impact of delineation variability on plan dosimetry. Despite seeing inter-observer variation within the context of the pre-trial benchmark cases the question remains as to whether this has any direct impact on the dose delivered to the target or OAR volumes. Two UK studies have assessed this; one utilising the IDEAL trial patient data set and the other the Isotoxic Lung pre-trial benchmark cases. Both studies investigated the impact inter-observer variation in OAR contouring had on radiotherapy plan dosimetry [71, 72].

The IDEAL trial dosimetry audit utilised sixty-six patient contour sets. Each patient's contours were assessed by the trial chief investigator and the trial RTTQA dosimetrist. Adjustments were made to the contours if there was agreement by the two assessors. Dose volume histograms (DVHs) were calculated for both the original and the edited volumes and then used to determine whether there was any difference in the isotoxic dose prescription. The results showed no changes to the prescription dose when editing the heart, brachial plexus or spinal cord PRV volumes. Seven out of sixty-six patients (10.6%) had differences in the final prescribed dose calculated due to changes in the oesophagus (4/66) and Lungs-GTV (3/66) outlining. They found that the mean difference in final prescribed dose was 0.6Gy (range: 0.2 – 1.1Gy) for oesophagus and 3.2Gy (2.5 – 4.5Gy) for lungs-GTV [71].

In the second study five prospective principal investigators for the Isotoxic Lung IMRT trial were recruited and each provided with an atlas of OAR contours. Each investigator, using the atlas, was asked to submit outlining cases which were then assessed for protocol compliance using the TMG consensus OAR contours. A total of twenty-five individual OAR contours were analysed including the spinal canal, brachial plexus, oesophagus, heart and mediastinal envelope. Comparing against the DVHs of the TMG consensus OARs the median difference in dose received by 1cc of the brachial plexus was 16.47% (IQR 50.40%), by 1cc of oesophagus 12.68%

(IQR 1.13%), by 1cc of heart 0.03% (IQR 0.06%) and by 1cc of mediastinal envelope 0.24% (IQR 0.02%). The difference in mean heart dose was 1.99% (IQR 1.01%). Overall, they found no difference in the final isotoxic prescription dose for any of the cases analysed [72].

These small studies suggest that inter-observer variation in OAR delineation can have an impact on both the final prescription dose and the dose received by the contoured OAR. This could have clinical implications if the difference was significant but was shown to be small in both these studies. Whether the same can be said for the head and neck and lung trial benchmark cases analysed here is not known but could form the basis of a future extension of this work.

Also leading on from this question is the potential impact inter-observer variation in OAR and target outlining can have both treatment toxicity and clinical outcomes. A future extension of this work might be to establish whether any correlation exists between high level of inter-observer variation during the pre-trial benchmark period and subsequent toxicity rates and clinical outcomes, including rates of local relapse, following completion and publication of the final trial results.

Finally, one question this research has not answered is whether the improvement radiotherapy quality assurance can have on clinician conformality during the pre-accrual benchmark period is maintained during the entire course of the radiotherapy trial. This would be an interesting question to study in a future extension of this work and might be answered by mandating that all participating clinicians must repeat a benchmark case exercise at pre-defined time points over the course of the trial recruitment period e.g. every 12 months. Analysis of these subsequent benchmark cases might establish whether inter-observer variation in target and OAR contouring deteriorates beyond the completion of the initial pre-trial benchmark period.

Appendix 1

Using Microsoft Excel 2016, I first created a grid where the first column represented the CT slice number and the second it's corresponding Z co-ordinate from the DICOM CT planning scan. Each row along the Z axis then effectively represented an individual CT slice from the DICOM CT dataset i.e.

CT Slice No.	CT Slice Z Number
1	-58.9
2	-58.7
3	-58.5
4	-58.3
5	-58.1
6	-57.9
7	-57.7
8	-57.5
9	-57.3
…	…
196	-19.9
197	-19.7
198	-19.5
199	-19.3
200	-19.1

The columns along the X axis represented the submitting PI's; each column representing a different clinician i.e.

PI No.								
1	2	3	4	5	…	16	17	18

Finally, the last column on the X axis always represented the tumour management group (TMG) reference contour (termed the 'gold standard') for the structure being analysed i.e.

Gold Standard

These elements were then combined to create a grid where each column on the X axis represented either a submitting clinician or the 'gold standard' and each row on the Z axis represented an individual CT slices from the pre-trial benchmark case CT dataset:

CT Slice No.	Z	PI No.																		Gold Standard
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
44	-50.3																			
45	-50.1																			
46	-49.9																			
47	-49.7																			
48	-49.5																			
49	-49.3																			
50	-49.1																			
51	-48.9																			
52	-48.7																			
53	-48.5																			
54	-48.3																			
55	-48.1																			
56	-47.9																			
57	-47.7																			
58	-47.5																			
59	-47.3																			
60	-47.1																			
61	-46.9																			
62	-46.7																			
63	-46.5																			
64	-46.3																			
65	-46.1																			
66	-45.9																			
67	-45.7																			
68	-45.5																			
69	-45.3																			
70	-45.1																			
71	-44.9																			
72	-44.7																			
73	-44.5																			
74	-44.3																			
75	-44.1																			
76	-43.9																			
77	-43.7																			
78	-43.5																			
79	-43.3																			
80	-43.1																			
81	-42.9																			
82	-42.7																			
83	-42.5																			
84	-42.3																			
85	-42.1																			
86	-41.9																			
87	-41.7																			
88	-41.5																			
89	-41.3																			
90	-41.1																			
91	-40.9																			
92	-40.7																			
93	-40.5																			

The example grid above comes from the first ART DECO pre-trial benchmark case. As can be seen, there were a total of 18 submitting clinicians plus the 'gold standard' (represented by individual columns along the X axis). The original planning CT dataset comprised a total of 200 individual CT slices but for this example, the grid above only demonstrates CT slice number 44 (Z = -50.3) to CT slice number 93 (Z = -40.5) (along the Z axis).

Using this grid, it was now possible to paste the L-CI data output from MATLAB into the Excel 2016 spreadsheet. MATLAB had created an individual L-CI file for each different structure analysed and this file contained L-CI data for each submitting clinician. The example below demonstrates the use of the grid to represent the brainstem L-CI data calculated using MATLAB for the first ART DECO pre-trial benchmark case:

CT Slice No.	Z	PI No.																		Gold Standard
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
44	-50.3																			
45	-50.1																			
46	-49.9																			
47	-49.7						0.00													
48	-49.5						0.00													
49	-49.3						0.00				0.00									
50	-49.1						0.00				0.00							0.00		
51	-48.9						0.00				0.00	0.00						0.00		
52	-48.7						0.00				0.00	0.00			0.00			0.00		
53	-48.5	0.00	0.00	0.00	0.00	0.00	0.83	0.00	0.00	0.34	0.90	0.84	0.00	0.00	0.74	0.84	0.00	0.70	0.00	1.00
54	-48.3	0.00	0.00	0.00	0.00	0.83	0.87	0.00	0.00	0.82	0.90	0.78	0.00	0.00	0.72	0.86	0.78	0.68	0.00	1.00
55	-48.1	0.50	0.43	0.32	0.00	0.79	0.83	0.00	0.37	0.76	0.90	0.79	0.00	0.00	0.70	0.86	0.72	0.67	0.00	1.00
56	-47.9	0.62	0.40	0.64	0.76	0.78	0.87	0.00	0.54	0.70	0.81	0.69	0.00	0.00	0.76	0.85	0.77	0.67	0.80	1.00
57	-47.7	0.91	0.41	0.88	0.87	0.82	0.88	0.00	0.56	0.83	0.87	0.71	0.84	0.84	0.83	0.88	0.86	0.76	0.90	1.00
58	-47.5	0.89	0.41	0.81	0.87	0.83	0.85	0.00	0.55	0.86	0.85	0.76	0.82	0.82	0.77	0.87	0.83	0.72	0.90	1.00
59	-47.3	0.79	0.36	0.85	0.77	0.77	0.78	0.00	0.56	0.71	0.77	0.67	0.76	0.76	0.68	0.79	0.83	0.66	0.79	1.00
60	-47.1	0.89	0.42	0.85	0.75	0.91	0.79	0.00	0.64	0.86	0.89	0.67	0.88	0.88	0.67	0.84	0.88	0.81	0.84	1.00
61	-46.9	0.78	0.51	0.71	0.75	0.85	0.57	0.00	0.81	0.84	0.78	0.52	0.77	0.77	0.64	0.84	0.81	0.86	0.76	1.00
62	-46.7	0.77	0.53	0.66	0.69	0.87	0.57	0.00	0.71	0.85	0.71	0.69	0.76	0.76	0.53	0.77	0.82	0.86	0.75	1.00
63	-46.5	0.74	0.53	0.79	0.63	0.81	0.51	0.00	0.64	0.90	0.68	0.58	0.75	0.75	0.57	0.70	0.84	0.84	0.73	1.00
64	-46.3	0.79	0.55	0.82	0.55	0.76	0.56	0.00	0.70	0.89	0.73	0.56	0.74	0.74	0.57	0.65	0.80	0.81	0.77	1.00
65	-46.1	0.83	0.56	0.85	0.55	0.68	0.67	0.00	0.69	0.83	0.85	0.65	0.73	0.73	0.56	0.67	0.75	0.77	0.79	1.00
66	-45.9	0.90	0.53	0.75	0.51	0.59	0.68	0.00	0.63	0.76	0.78	0.55	0.75	0.75	0.55	0.75	0.81	0.73	0.74	1.00
67	-45.7	0.89	0.50	0.81	0.49	0.53	0.73	0.55	0.66	0.73	0.54	0.58	0.70	0.70	0.54	0.72	0.81	0.68	0.68	1.00
68	-45.5	0.71	0.47	0.81	0.41	0.51	0.70	0.51	0.60	0.57	0.45	0.35	0.51	0.51	0.55	0.63	0.75	0.64	0.59	1.00
69	-45.3	0.56	0.45	0.70	0.44	0.50	0.69	0.52	0.63	0.61	0.43	0.39	0.42	0.42	0.51	0.57	0.73	0.64	0.50	1.00
70	-45.1	0.59	0.43	0.74	0.40	0.50	0.72	0.52	0.53	0.47	0.43	0.32	0.42	0.42	0.47	0.57	0.75	0.63	0.48	1.00
71	-44.9	0.60	0.44	0.75	0.41	0.49	0.69	0.51	0.62	0.41	0.45	0.36	0.45	0.45	0.42	0.56	0.83	0.61	0.39	1.00
72	-44.7	0.62	0.44	0.83	0.46	0.50	0.80	0.56	0.65	0.52	0.48	0.45	0.54	0.54	0.47	0.56	0.80	0.61	0.36	1.00
73	-44.5	0.63	0.43	0.83	0.50	0.48	0.81	0.54	0.58	0.53	0.51	0.55	0.55	0.55	0.48	0.61	0.80	0.59	0.31	1.00
74	-44.3	0.67	0.51	0.72	0.57	0.55	0.75	0.49	0.69	0.68	0.61	0.53	0.67	0.67	0.53	0.75	0.71	0.63	0.31	1.00
75	-44.1	0.69	0.58	0.52	0.55	0.55	0.74	0.42	0.48	0.59	0.67	0.52	0.71	0.71	0.56	0.66	0.58	0.63	0.35	1.00
76	-43.9	0.67	0.71	0.00	0.57	0.61	0.60	0.35	0.47	0.66	0.71	0.51	0.77	0.77	0.58	0.59	0.00	0.64	0.41	1.00
77	-43.7	0.59	0.84	0.00	0.74	0.63	0.60	0.29	0.58	0.69	0.74	0.47	0.73	0.73	0.64	0.70	0.00	0.63	0.46	1.00
78	-43.5	0.66	0.86	0.00	0.00	0.00	0.61	0.24	0.60	0.73	0.77	0.28	0.72	0.72	0.60	0.70	0.00	0.63	0.50	1.00
79	-43.3	0.00	0.00				0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00		0.00	0.00	
80	-43.1	0.00	0.00				0.00	0.00	0.00		0.00	0.00	0.00	0.00				0.00	0.00	
81	-42.9						0.00		0.00			0.00							0.00	
82	-42.7								0.00										0.00	
83	-42.5								0.00										0.00	
84	-42.3																		0.00	
85	-42.1																		0.00	
86	-41.9																		0.00	
87	-41.7																		0.00	
88	-41.5																		0.00	
89	-41.3																		0.00	
90	-41.1																		0.00	
91	-40.9																			
92	-40.7																			
93	-40.5																			

Finally, to increase the ease of visual interpretation of the data, the L-CI data was 'colour coded' using the conditional formatting tool within Microsoft Excel 2016. Conditional formatting in Excel enables you to highlight cells with a certain colour, depending on the cell's value. For the purposes of the L-CI data this colour highlighting was defined as:

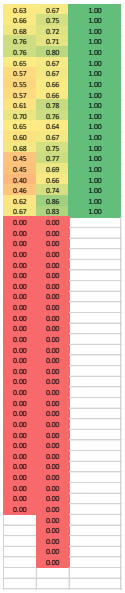
- No Conformity i.e. contour not present (L-CI = 0.00)
- Poor conformity
- Good conformity
- Perfect conformity (L-CI = 1.00)

Again, using the brainstem L-CI data from the first ART DECO pre-trial benchmark case as an example, applying conditional formatting using the above rules, the data becomes visually easier to interpret:

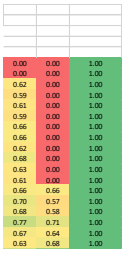
CT Slice No.	z	PI No.																		Gold Standard
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
44	-50.3																			
45	-50.1																			
46	-49.9																			
47	-49.7						0.00													
48	-49.5						0.00													
49	-49.3						0.00				0.00									
50	-49.1						0.00				0.00							0.00		
51	-48.9						0.00				0.00	0.00						0.00		
52	-48.7						0.00				0.00	0.00			0.00			0.00		
53	-48.5	0.00	0.00	0.00	0.00	0.00	0.83	0.00	0.00	0.34	0.90	0.84	0.00	0.00	0.74	0.84	0.00	0.70	0.00	1.00
54	-48.3	0.00	0.00	0.00	0.00	0.83	0.87	0.00	0.00	0.82	0.90	0.78	0.00	0.00	0.72	0.86	0.78	0.68	0.00	1.00
55	-48.1	0.50	0.43	0.32	0.00	0.79	0.83	0.00	0.37	0.76	0.90	0.79	0.00	0.00	0.70	0.86	0.72	0.67	0.00	1.00
56	-47.9	0.62	0.40	0.64	0.76	0.78	0.87	0.00	0.54	0.70	0.81	0.69	0.00	0.00	0.76	0.85	0.77	0.67	0.80	1.00
57	-47.7	0.91	0.41	0.88	0.87	0.82	0.88	0.00	0.56	0.83	0.87	0.71	0.84	0.84	0.83	0.88	0.86	0.76	0.90	1.00
58	-47.5	0.89	0.41	0.81	0.87	0.83	0.85	0.00	0.55	0.86	0.85	0.76	0.82	0.82	0.77	0.87	0.83	0.72	0.90	1.00
59	-47.3	0.79	0.36	0.85	0.77	0.77	0.78	0.00	0.56	0.71	0.77	0.67	0.76	0.76	0.68	0.79	0.83	0.66	0.79	1.00
60	-47.1	0.89	0.42	0.85	0.75	0.91	0.79	0.00	0.64	0.86	0.89	0.67	0.88	0.88	0.67	0.84	0.88	0.81	0.84	1.00
61	-46.9	0.78	0.51	0.71	0.75	0.85	0.57	0.00	0.81	0.84	0.78	0.52	0.77	0.77	0.64	0.84	0.81	0.86	0.76	1.00
62	-46.7	0.77	0.53	0.66	0.69	0.87	0.57	0.00	0.71	0.85	0.71	0.69	0.76	0.76	0.53	0.77	0.82	0.86	0.75	1.00
63	-46.5	0.74	0.53	0.79	0.63	0.81	0.51	0.00	0.64	0.90	0.68	0.58	0.75	0.75	0.57	0.70	0.84	0.84	0.73	1.00
64	-46.3	0.79	0.55	0.82	0.55	0.76	0.56	0.00	0.70	0.89	0.73	0.56	0.74	0.74	0.57	0.65	0.80	0.81	0.77	1.00
65	-46.1	0.83	0.56	0.85	0.55	0.68	0.67	0.00	0.69	0.83	0.85	0.65	0.73	0.73	0.56	0.67	0.75	0.77	0.79	1.00
66	-45.9	0.90	0.53	0.75	0.51	0.59	0.68	0.00	0.63	0.76	0.78	0.55	0.75	0.75	0.55	0.75	0.81	0.73	0.74	1.00
67	-45.7	0.89	0.50	0.81	0.49	0.53	0.73	0.55	0.66	0.73	0.54	0.58	0.70	0.70	0.54	0.72	0.81	0.68	0.68	1.00
68	-45.5	0.71	0.47	0.81	0.41	0.51	0.70	0.51	0.60	0.57	0.45	0.35	0.51	0.51	0.55	0.63	0.75	0.64	0.59	1.00
69	-45.3	0.56	0.45	0.70	0.44	0.50	0.69	0.52	0.63	0.61	0.43	0.39	0.42	0.42	0.51	0.57	0.73	0.64	0.50	1.00
70	-45.1	0.59	0.43	0.74	0.40	0.50	0.72	0.52	0.53	0.47	0.43	0.32	0.42	0.42	0.47	0.57	0.75	0.63	0.48	1.00
71	-44.9	0.60	0.44	0.75	0.41	0.49	0.69	0.51	0.62	0.41	0.45	0.36	0.45	0.45	0.42	0.56	0.83	0.61	0.39	1.00
72	-44.7	0.62	0.44	0.83	0.46	0.50	0.80	0.56	0.65	0.52	0.48	0.45	0.54	0.54	0.47	0.56	0.80	0.61	0.36	1.00
73	-44.5	0.63	0.43	0.83	0.50	0.48	0.81	0.54	0.58	0.53	0.51	0.55	0.55	0.55	0.48	0.61	0.80	0.59	0.31	1.00
74	-44.3	0.67	0.51	0.72	0.57	0.55	0.75	0.49	0.69	0.68	0.61	0.53	0.67	0.67	0.53	0.75	0.71	0.63	0.31	1.00
75	-44.1	0.69	0.58	0.52	0.55	0.55	0.74	0.42	0.48	0.59	0.67	0.52	0.71	0.71	0.56	0.66	0.58	0.63	0.35	1.00
76	-43.9	0.67	0.71	0.00	0.57	0.61	0.60	0.35	0.47	0.66	0.71	0.51	0.77	0.77	0.58	0.59	0.00	0.64	0.41	1.00
77	-43.7	0.59	0.84	0.00	0.74	0.63	0.60	0.29	0.58	0.69	0.74	0.47	0.73	0.73	0.64	0.70	0.00	0.63	0.46	1.00
78	-43.5	0.66	0.86	0.00	0.00	0.00	0.61	0.24	0.60	0.73	0.77	0.28	0.72	0.72	0.60	0.70	0.00	0.63	0.50	1.00
79	-43.3	0.00	0.00				0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00		0.00	0.00	
80	-43.1	0.00	0.00				0.00	0.00	0.00		0.00	0.00	0.00	0.00				0.00	0.00	
81	-42.9						0.00		0.00			0.00							0.00	
82	-42.7								0.00										0.00	
83	-42.5								0.00										0.00	
84	-42.3																		0.00	
85	-42.1																		0.00	
86	-41.9																		0.00	
87	-41.7																		0.00	
88	-41.5																		0.00	
89	-41.3																		0.00	
90	-41.1																		0.00	
91	-40.9																			
92	-40.7																			
93	-40.5																			

Key: No Conformity i.e. contour not present (L-CI = 0.00); Poor conformity; Good conformity; Perfect conformity (L-CI = 1.00)

With the application of conditional formatting, it now makes it visually easier to appreciate areas of over outlining:



Under outlining:



Higher levels of L-CI agreement (range 0.63 – 0.88):

0.73	0.82	0.63	1.00
0.72	0.84	0.70	1.00
0.70	0.78	0.70	1.00
0.88	0.84	0.78	1.00
0.83	0.78	0.73	1.00
0.80	0.77	0.73	1.00
0.76	0.74	0.71	1.00
0.75	0.76	0.71	1.00
0.78	0.80	0.71	1.00
0.82	0.79	0.69	1.00

Lower levels of L-CI agreement (range 0.41 – 0.59):

0.44	0.55	0.41	1.00
0.51	0.72	0.49	1.00
0.48	0.59	0.45	1.00
0.47	0.55	0.44	1.00
0.57	0.61	0.54	1.00
0.50	0.56	0.47	1.00
0.51	0.58	0.56	1.00
0.52	0.55	0.59	1.00
0.49	0.54	0.54	1.00
0.49	0.56	0.54	1.00
0.52	0.49	0.54	1.00
0.51	0.57	0.54	1.00
0.52	0.57	0.52	1.00

For some of the structures analysed, clinicians had also failed to submit a contour all together. In the example below, clinician number 2 has failed to submit a CTV1 contour for analysis and hence the column is empty.

CT Slice No.	z	PI No.									Gold Standard
		1	2	3	4	5	6	7	8	9	
45	-0.60						0.00				
46	-0.30						0.00				
47	0.00						0.00				
48	0.30				0.00	0.00	0.00				
49	0.60	0.74		0.74	0.57	0.75	0.38	0.23	0.84	0.00	1.00
50	0.90	0.60		0.65	0.60	0.82	0.66	0.29	1.00	0.68	1.00
51	1.20	0.64		0.67	0.68	0.83	0.74	0.51	1.00	0.75	1.00
52	1.50	0.68		0.64	0.71	0.86	0.74	0.69	0.93	0.79	1.00
53	1.80	0.72		0.68	0.75	0.90	0.75	0.73	0.90	0.82	1.00
54	2.10	0.73		0.69	0.78	0.91	0.76	0.78	0.87	0.81	1.00
55	2.40	0.74		0.66	0.74	0.90	0.71	0.81	0.84	0.85	1.00
56	2.70	0.76		0.74	0.65	0.87	0.60	0.82	0.70	0.82	1.00
57	3.00	0.80		0.71	0.68	0.87	0.60	0.80	0.71	0.78	1.00
58	3.30	0.82		0.67	0.72	0.85	0.54	0.81	0.76	0.80	1.00
59	3.60	0.81		0.66	0.75	0.84	0.57	0.84	0.82	0.85	1.00
60	3.90	0.82		0.74	0.80	0.82	0.59	0.84	0.85	0.89	1.00
61	4.20	0.85		0.84	0.85	0.81	0.60	0.79	0.89	0.88	1.00
62	4.50	0.87		0.89	0.85	0.83	0.74	0.77	1.00	0.88	1.00
63	4.80	0.84		0.94	0.85	0.91	0.72	0.76	1.00	0.87	1.00
64	5.10	0.78		0.93	0.83	0.91	0.82	0.83	1.00	0.87	1.00
65	5.40	0.76		0.91	0.84	0.91	0.82	0.87	1.00	0.89	1.00
66	5.70	0.79		0.90	0.83	0.88	0.83	0.85	1.00	0.89	1.00
67	6.00	0.88		0.90	0.79	0.78	0.80	0.75	1.00	0.88	1.00
68	6.30	0.87		0.79	0.78	0.86	0.79	0.79	1.00	0.90	1.00
69	6.60	0.88		0.77	0.77	0.87	0.81	0.79	1.00	0.92	1.00
70	6.90	0.82		0.77	0.77	0.84	0.75	0.75	1.00	0.87	1.00
71	7.20	0.81		0.89	0.80	0.63	0.89	0.00	1.00	0.65	1.00
72	7.50	0.66		0.84	0.63	0.62	0.80	0.00	1.00	0.80	1.00
73	7.80	0.00		0.78	0.33	0.00	0.83	0.00	1.00	0.00	1.00

Key: No Conformity i.e. contour not present (L-CI = 0.00); Poor conformity; Good conformity; Perfect conformity (L-CI = 1.00)

By slightly modifying the layout of the grid, substituting each PI column with re-submissions by the same PI, it was also possible to visually demonstrate the changes made to a structure over the course of subsequent re-submissions.

The example below demonstrates how the CTV1, left parotid, right parotid, brainstem and spinal cord volumes for a single PI evolved over the course of a total of 3 submissions during the ART-DECO trial:

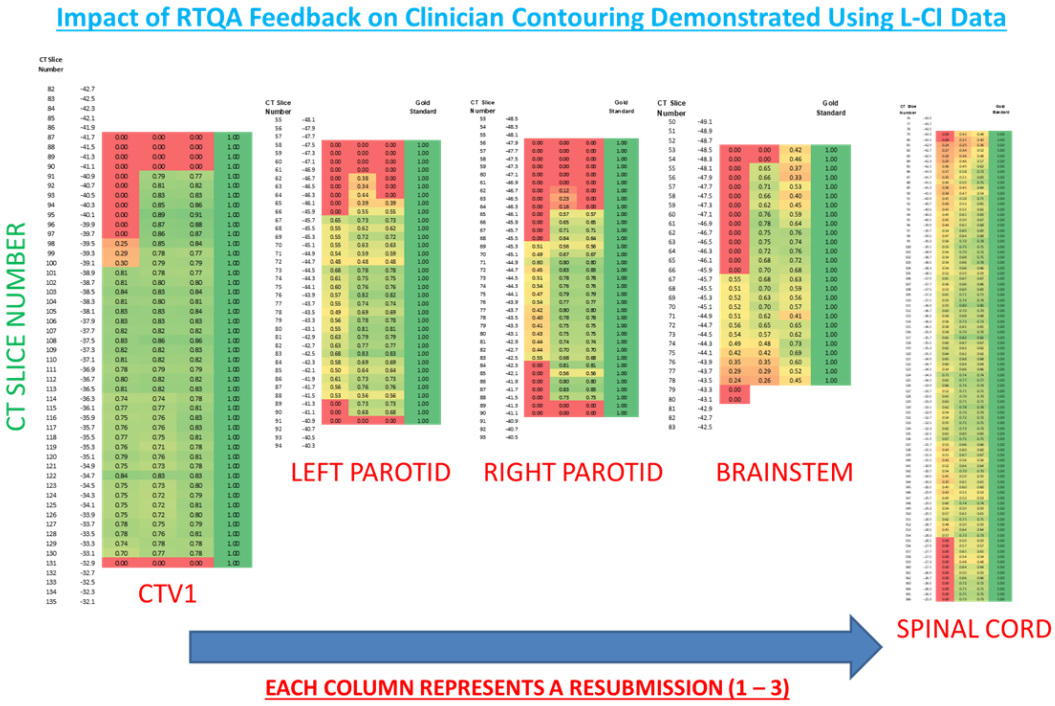


Figure 25: Example to Show How an Individual PI's L-CI Data for Several Structures Changes Over the Course of Three Submissions (ART-DECO Trial) (No Conformity i.e. contour not present (L-CI = 0.00); Poor conformity; Good conformity; Perfect conformity (L-CI = 1.00))

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