PROJECT TITLE: Evaluation of a novel head and neck immobilization device for external beam radiation therapy

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SUMMARY:

The purpose of this study was to compare the novel CDR Systems MayoMold to the Civco Medical Solutions standard neck roll in order to determine if the MayoMold should become widely used for head and neck cancer radiation therapy immobilization at CancerCare Manitoba.
Fifteen patients were enrolled in the standard neck roll cohort and ten patients were enrolled in the MayoMold cohort. Bony landmarks of clinical interest were selected and daily imaging was used to quantify daily changes in patient set up and deformations with respect to the digitally reconstructed radiograph created from each patient's planning CT. Bayesian statistics were employed with support from Epidemiology at CancerCare Manitoba in order to compare the patients to themselves across all of their treatment fractions, to different patients in the same cohort, and to the other cohort. Subjective end points concerning the MayoMold were solicited from patients and staff.
Several measures of patient immobilization, especially concerning the mandible, were found to be inferior in the MayoMold cohort. These results were statistically significant but not clinically significant, allowing the conclusion to be made that the MayoMold was not superior to the standard neck roll with regards to patient immobilization. Adverse subjective feedback and the increased cost of using the MayoMold skewed the subjective end points towards the negative.
In all, it was not recommended that CancerCare Manitoba adopt the MayoMold.

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Student's Signature

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Introduction

More than two hundred patients are treated annually at CancerCare Manitoba with external beam radiation therapy for head and neck, CNS, and spine tumours. Through the course of treatment, patients must remain still for up to twenty-five minutes per fraction for up to thirty five treatment fractions. Ensuring that the position of patients is maintained for the duration of fractionated radiation therapy is critical, especially in the head and neck region[1]. In order to facilitate reproducible yet reasonably comfortable treatment, head and neck immobilization devices are used for these patients. At CancerCare Manitoba, patients are immobilized with a custom thermoplastic mask and a standard neck roll.

Informal analysis of daily imaging by CancerCare Manitoba staff and clinicians suggests that this method of immobilization may cause clinically significant changes in the position of the patient, especially in the region of the mandible. The observed positional changes of the mandible are the result of deformation of the patient which cannot be fully compensated for through transformational adjustment in the orthogonal planes, resulting in reduced accuracy of the external beam radiation therapy with respect to the planned treatment volume.

The novel head and neck immobilization device this study investigates, the CDR Systems MayoMold (see Figure 1), replaces the standard neck roll. The MayoMold is made of foam which expands around the patient and hardens to produce a customized immobilization system for the shoulders, neck, and head. In order to justify the increased cost associated with using the MayoMold for standard treatment of head and neck patients, its objective and subjective merits must be considered and be found on the whole superior to the present immobilization system. Objective measures include patient position and deformation through the course of treatment, while subjective assessment can be made with the less scientifically stringent softer end points of cost effectiveness, staff ease of use and perception of patient comfort, and patient feedback.

Recent studies have compared two commercially available systems of immobilization for patient immobilization capability and cost efficiency, indicating this is an area of active scientific interest[2,3].

At CancerCare Manitoba, treatment margins, which are interpreted as “safety margins” added to radiation therapy plans to ensure all targeted tissue is properly irradiated in most patients, are five millimetres. One of the methods used to estimate the appropriate treatment margin is the van Herk equation which produces a treatment margin that yields a minimum dose of at least 95% of planned dose to the clinical target volume in 90% of patients[4]. The linearized equation which forms a lower limit to appropriate treatment margins is given as:

$$\textbf{Margin (planning target volume)} = 2.5\Sigma + 0.7\sigma$$

Where Σ is the total standard deviation of the systematic error and σ is the total standard deviation of the random error[4].

The former, the systematic error, Σ, is intrinsic to each patient and present throughout the course of radiation treatment yet variable through a population of patients, while the latter, σ, is best understood as execution or set-up error which is variable from day-to-day for each individual patient and the entire group of patients. Both Σ and σ can be estimated based on measurements taken from daily imaging of patients. The systematic error, Σ, is estimated by finding the mean of every patient's measured shift through each fraction in a given location and taking the standard deviation of those means. The random error, σ, is estimated by finding the standard deviation of every patient's measured shift through each fraction in a given location and taking the root mean square of those standard deviations[5].

This study examines the characteristics of the MayoMold immobilization device and compares them to the standard neck roll by measuring changes in patient transformation and patient deformation relative to the digitally reconstructed radiograph (DRR), which is reconstructed from the treatment planning CT and is used as the gold standard for patient position set up through the course of radiation therapy.

Patient set up errors and the position of the mandible and other selected points of interest as described in the methods section, which represent the transformational and deformational differences respectively between the daily imaging and the DRR, as well as the effect of time related changes to the patient, including weight loss, measured by using fraction number as a proxy for time progression will all be investigated for the MayoMold cohort and the standard neck roll cohort.

It is hypothesized that because of the custom nature of the MayoMold, it will provide better overall patient immobilization with particularly improved immobilization in the area of the mandible, while providing at least comparable patient comfort and staff ease of use.

Materials and Methods

After receiving ethics approval from the University of Manitoba's Health Research Ethics Board to perform this study, fifteen consecutive previously treated patients with head and neck malignancies who received external beam radiation therapy were enrolled into the retrospective cohort. The retrospective cohort used a "Disposable TYPE S Klarity Green IMRT reinforced" thermoplastic mesh mask and standard neck roll, both from Civco Medical Solutions. Initially, ten consecutive new patients were enrolled in the experimental arm of the study which used the same thermoplastic mesh mask but replaced the standard neck roll with the CDR Systems MayoMold. However, one of the patients in the MayoMold cohort had severe issues with claustrophobia and weight loss through the course of treatment and required extensive modification of their immobilization device. Neither patients in the retrospective cohort nor any other patients in the MayoMold cohort experienced similar issues, so the data from this patient was censored from statistical analysis and an eleventh patient was enrolled in the MayoMold cohort to bring the total number of analyzed patients back to ten. To reduce variability in levels of staff familiarity with the MayoMold, all of the MayoMold patients received treatment on the same IMRT machine with a smaller subset of the total radiation therapy staff assigned to that machine. Broadly speaking, the retrospective standard neck roll cohort acted as a control to the MayoMold cohort.

In both groups, each patient was imaged with computed tomography (CT) in order to plan treatment. From this CT a DRR was made in the lateral and anterior positions. Standard procedure was for staff to compare daily lateral and anteroposterior plain imaging or, approximately once per week, a Cone Beam CT (CBCT) to the corresponding DRR and to adjust couch position in order to preferentially match the bony anatomy of the cervical spine to the DRR as closely as possible, at the expense of poorer matching of other areas of head and neck anatomy. Couch position could be changed in four different ways: vertically (VRT), longitudinally (LNG), and laterally (LAT), corresponding to three degrees of orthogonal translational freedom as well as rotationally (RTN), corresponding to a rotation around the longitudinal axis running between the head and feet of the patient. The values for these four patient set up variables were automatically recorded for each treatment fraction and were exported from the Varian Offline Review software.

The lateral x-ray, or weekly CBCT viewed in the sagittal plane, generated with each treatment fraction, as described above, was analyzed by the student after the patient received treatment. As shown in Figure 2, four bony landmarks, points Alpha through Delta corresponding, respectively, as closely as possible to the anterior and inferior portion of C2, the anterior and superior portion of C5, the mental process of the mandible, and the hard palate were selected for each patient. The angles between these points were labeled α, α`, β, γ, γ`, and δ, as shown in Figure 2. Sides were labeled according to the angle opposite them, except for side γ which was not labeled. These points were selected in order to demonstrate and quantify mandibular and other movement, such as head and neck flexion and extension. Some of the points, such as side γ between C2 and C5, were expected to show very small changes from day to day and act as an internal check to this method of patient deformation measurement. Other points, however, such as the point on the mental process of the mandible, were chosen to capture what was subjectively and anecdotally believed to be the area of greatest variability and deviation from the DRR.

Every patient received between thirty and thirty-five external beam radiation treatment fractions, at the rate of approximately one per day. Each of the lateral x-rays or sagittal views of the weekly CBCTs corresponding to each treatment fraction was labeled in a similar manner and had every named angle and side measured. Similarly, every DRR was labeled and had every named angle and side measured as well. This process generated more than seven hundred fifty labeled lateral x-rays or sagittal CBCTs which produced a dataset of some size for the twenty five patients.

Quantification of intra-patient deformation from fraction to fraction was performed by comparing the side lengths and angles for every fraction to the same side lengths and angles found in the DRR, which was used as a standard for that patient because of its previous use in treatment planning. The use of the DRR as the standard against which to compare daily imaging has been used in previous literature for similar purposes[6]. Additionally, comparison was performed between patients in the same cohort by comparing differences from the DRR for each patient in order to assess the device used in that cohort. Inter-patient variations in anatomy, most notably the visibility of lower cervical vertebra in the lateral x-rays, were of diminished importance because of the intra-patient comparison of every lateral image to the patient’s own DRR prior to inter-patient comparison. Finally, comparison was made between the standard neck roll cohort and the MayoMold cohort based on the inter-patient data of the two cohorts.

After the data was collected, statistical support was provided by Epidemiology at CancerCare Manitoba. Through consultation with a statistician, it was determined that the experimental design was likely to be best served by statistical examination through the use of Bayesian statistics as opposed to the more commonly used frequentist statistics.

In Bayesian statistics, prior probabilities are selected to have an influence on the value θ, which is the estimate of the parameter. Using Bayes' theorem, the prior probabilities are combined with the information found in the raw data to find a posterior probability which forms the basis for all decisions made about θ[7]. In practical terms for the output of this study, the posterior probability distribution produced Bayesian credible intervals (BCI) for the parameter estimate, which were the intervals that were required to ensure that 95% of the time the mean would be contained in the interval, without reference to the distribution of the sample[8].

There were a number of useful advantages to these statistics in the context of this study. The study results were less susceptible to sample size issues related to the number of variables examined because Bayesian statistics produce a posterior distribution that does not change depending on the way it is analyzed[8]. Had the data been analyzed by frequentist methods, the level of the p-value that would determine statistical significance for the nine examined side lengths and angles would have to have been changed in order to reduce the probability of finding significance due to chance alone, which would have likely resulted in no statistically significant findings given the sample size or required that fewer variables be examined. Additionally, Bayesian credible intervals provide more useful information than merely accepting or rejecting the null hypothesis[8]. In this study, the additional information from Bayesian credible intervals was used to test whether or not clinical significance, defined by a mean deviation of greater than two millimetres, was achieved in any side length in either cohort. This definition of clinical significance, well below the size of treatment margins, is justified in the discussion. Finally, the Bayesian statistics employed are more suited to customized modeling and are computationally more robust with the ability to use data that would normally violate statistical assumptions[8].

The primary criticism of Bayesian analysis revolves around the selection of prior probabilities. The choice of priors is critical and must be grounded in evidence as priors can have a large influence on the posterior probability, especially in studies with small amounts of data[7]. Since there was no convincing evidence available to justify selection of any strong priors, the priors selected for this study were chosen to be weak and non-influential on the final computed posterior probability in order to gain the benefits of Bayesian statistics without the significant drawback of arbitrarily biasing the final result.

The statistician used a random intercept model for the longitudinal analysis of absolute deviations between the MayoMold and the standard neck roll. A Markov chain Monte Carlo generalized linear mixed models (MCMCglmm) package in R was used. The systematic and random error was compared with a Bayesian t-test in R, based on a model found in recent literature[9].

Subjective feedback from the clinician, staff, and patients was solicited via non-rigorous means with the intent to provide an impression of the suitability of the MayoMold at CancerCare

Manitoba. The feedback was based on the softer end points of patient comfort, staff ease of use, and overall clinician opinion of the progress made by patients enrolled in the MayoMold cohort.

Results

The results computed after the Bayesian statistical analyses are shown in Tables 1 and 2. Nine areas of interest were investigated. The first four areas, VRT, LNG, LAT, and RTN, corresponded to the patient set up errors in the vertical, longitudinal, and lateral directions and the rotational plane around the longitudinal axis for the supine patient. The latter five areas, Angle Alphas, which was formed by Angle Alpha plus Angle Alpha`, Side Alpha, Side Gamma, Side Alpha`, and Side Gamma`, correspond to the differences found between patient imaging and the DRR due to deformation for the given location in Figure 2.

Table 1 contains data from two analyses between each cohort for each location. The MayoMold rows find the mean difference between the MayoMold cohort and the standard neck roll cohort at a given location and quote the corresponding 95% Bayesian Credible Interval and the p-value, which behaves as a normal p-value and indicates the probability of finding this difference by chance alone. A p-value of less than 0.05 is considered significant. Attention should be drawn to the two values which are statistically significant: Side Alpha (0.117 cm, 0.00200 - 0.234 cm) and Side Gamma` (0.127 cm, 0.0103 – 0.244 cm). Side Alpha corresponds to the side length between the lower cervical spine and the mental process of the mandible while Side Gamma` corresponds to the side length between C2 and the hard palate. As these values are positive, they imply that for these side lengths the MayoMold displayed a greater difference relative to the matched DRR than the standard neck roll, which implies less immobilization of neck flexion and extension and mandible position with the MayoMold. While the extreme tail of both locations' credible interval reaches above two millimetres, which is the assigned value for clinical significance, the most probable means and the majority of the estimates of the mean are below the level of clinical significance. It must also be noted that this table only provides a comparison between the means of the two systems and does not reference absolute deviation or the components of Systematic or Random Error, which are found in Table 2.

The Fraction Number rows of Table 1 find the mean difference between the MayoMold cohort and the standard neck roll cohort at a given location when the progression of time, as measured by the fraction number, is considered. A positive number indicates that the MayoMold became less effective at immobilization, relative to the standard neck roll, as time progressed. Attention should be drawn to the three statistically significant length measurements. In all of them, the MayoMold provided less immobilization relative to the standard neck roll as time progressed: LNG, Side Alpha, and Side Alpha`. Despite being statistically significant, browsing the mean differences and 95% BCIs shows that these values are not clinically significant as not even the most extreme range of the credible intervals come close to the level of clinical significance, defined as two millimetres.

Table 2 characterizes the Systematic and Random Error for each of the areas of interest in absolute terms and then compares them. The Mean Difference column describes any difference in Systematic and Random Error for a given location and produces a 95% BCI. No p-values are given because all of these credible intervals cross zero and therefore none of these differences are statistically significant, which implies that no statistically significant difference between the MayoMold and the standard neck roll exists when the component errors are compared individually.

Despite this, the absolute means are also useful data to examine in order to ensure that patient immobilization is actually occurring with both systems and that the finding of no statistically significant difference between the two cohorts is not simply a failure to detect areas in which both systems are performing equally poorly at patient immobilization. All of individual components of the Mean Difference column in Table 2 for the Systematic Error are less than the defined clinically significant value of two millimetres, indicating no obvious intrinsic problems with patient immobilization which recurred in every treatment fraction in either the MayoMold or the standard neck roll.

However, in the Random Error rows of Table 2, which represent day to day errors in patient set up and deformation, the same sides highlighted for Table 1, Sides Alpha (0.282 cm) and Gamma` (0.239 cm), had means greater than two millimetres for the MayoMold. Side Alpha (0.268 cm) also had a mean greater than two millimetres for the standard neck roll. While this study was designed as a comparison rather than as an audit of absolute performance, it is suitable to note that the informal analysis of difficulty achieving immobilization of the mandible which prompted this study was not unfounded, as Side Alpha, which demonstrates the greatest day to day errors in deformation, is the side length which most closely corresponds to mandible position.

Subjective feedback from the clinician, staff, and patients was solicited non-rigorously and thus must be considered as low level evidence. Nonetheless, the staff reported that the MayoMold took longer and was more difficult to set up. Additionally, the staff perceived that patients were less comfortable during set up and treatment. The clinician reported that MayoMold patients typically had a longer adjustment phase to the immobilization process and more complaints of claustrophobia. Additionally, the cost of the MayoMold is significantly more than the cost of the standard neck roll, especially when scaled to the annual treatment population of CancerCare Manitoba.

Discussion

In order to estimate the degree of patient movement and deformation permitted by the MayoMold conservatively and err on the side of patient safety, a value of two millimetres was chosen prior to reviewing the output data as the level that the most probable mean difference would have to surpass in order to indicate a potentially clinically significant side length difference for any investigated location. This value was chosen well below the CancerCare Manitoba treatment margin of five millimetres because it is conceivable that multiple errors in a single patient at different locations could add together absolutely or compound upon each other to produce a larger total error.

In summary of the results, for most parameters there was no statistically significant difference between the MayoMold and the standard neck roll. There were some statistically significant areas where the MayoMold performed inferiorly to the standard neck roll, but not to the level of clinical significance. These areas of statistical significance without clinical significance included some of the comparisons of mean difference as time progressed by fraction number and the simple comparison between the means of the sides which correspond to mandibular and neck flexion and extension immobilization. These simple comparisons between the means, however, are only one measure of a relative comparison between the two cohorts and do not give as much useful information as the comparisons between Systematic and Random Errors as they cannot be readily transformed into appropriate treatment safety margins by use of the van Herk formula.

The final result of note was the large mean Random Error in the region of the mandible above the defined level of clinical significance for both the MayoMold and the standard neck roll. No statistical significance was found between the Random Errors for this location likely because both systems performed approximately equally poorly in this region, which would be in line with the informal observations of large deformations in the area of the mandible which prompted this study. Thus, concern about reproducibility of patient mandibular position should be considered in future patient immobilization audits or research.

That there is no definitive clinically significant difference between the MayoMold and the standard neck roll is in line with a June 2012 abstract which reported the preliminary result that between the MayoMold and the Civco Type-S immobilization device "minimal difference in the [cervical] spine and mandible reproducibility" existed[10].

It is believed that a larger patient population would be unlikely to produce a different, clinically significant result in favour of the MayoMold and change the final recommendation of this study. The use of Bayesian statistics allowed for Bayesian credible intervals to be made which estimated the most probable location of the mean for any given parameter. Given that the mean differences of the statistically significant areas of difference between the MayoMold and the standard neck roll all suggested inferior immobilization with the MayoMold and tended to be gathered well below the level of defined clinical significance and far below the present treatment margins, it is expected that adding further data to the study would merely reduce the size of the Bayesian credible intervals while not impressively shifting the location of the most probable means of the data or changing the conclusions of the study.

While not rigorously collected, the adverse subjective feedback from staff and patients and the intrinsic disadvantage associated with the greater cost of the MayoMold contribute to an overall negative impression in the holistic and subjective assessment of the MayoMold.

In conclusion, based on measurements of clinically relevant parts of patient anatomy taken from daily imaging, use of the MayoMold by Radiation Therapy staff who are relatively new to the MayoMold device cannot be shown to be superior in a clinically significantly way to the presently used standard neck roll. There is the possibility that increased staff familiarity with the device could cause better results given the customized nature of the MayoMold and the user-dependent process of expanding the constitutive foam, but the cost of such an experimental learning period is prohibitive and not practical.

In the absence of convincing objective patient position data that the MayoMold is superior to the standard neck roll when used by the staff at CancerCare Manitoba, the subjective considerations of cost and staff and patient perceptions which skew towards the negative suggest that the MayoMold should not be recommended for wider use at CancerCare Manitoba.

Further research in this area of study could include examining other systems of immobilization which have a focus on the region of the mandible, which has been incidentally noted by this study to be an area of some concern. Novel mechanisms of immobilization potentially worth examining may include devices that have a patient bite system that is referenced to the treatment couch or the patient's thermoplastic mask. Additionally, ongoing surveillance of head and neck external beam radiation therapy patients could be useful to more accurately characterize the required treatment margins with the ultimate hope of being able to safely justify a reduction of the five millimetre margin which would yield a substantial improvement in sparing of normal tissue[11].

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Figures and Tables

Figure 1: A MayoMold Head and Neck Immobilization Device after use at CancerCare Manitoba.

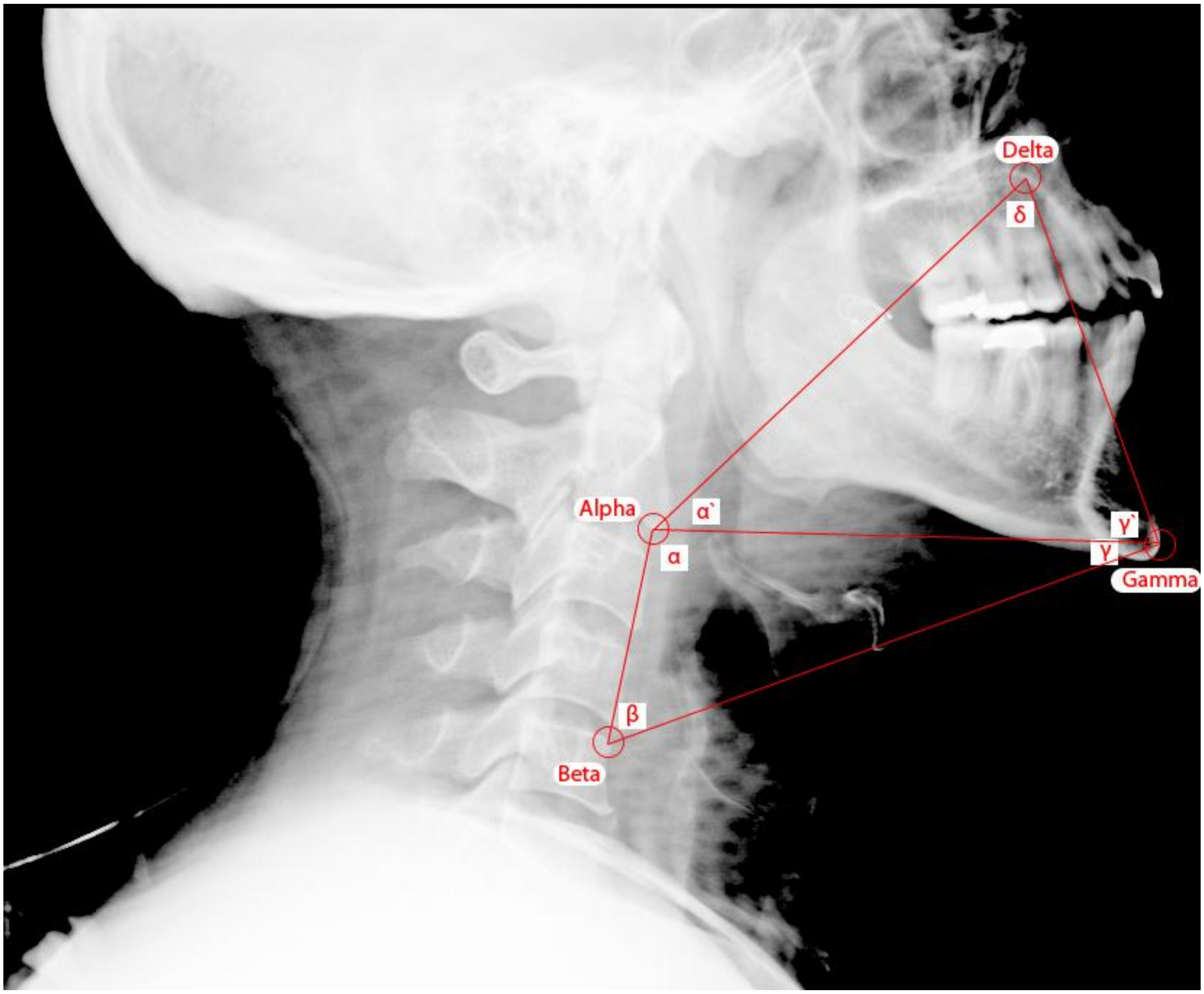

Figure 2: Labeled lateral X-Ray demonstrating two triangles created from the four selected landmark points superimposed on the bony anatomy, producing five side measurements and six angle measurements

Table 1: Difference between means for MayoMold and standard neck roll cohorts when compared overall and by time progression				
Location Measured	**Comparison**	**Mean Difference (cm)***	**95% BCI (cm)****	**p**
VRT	MayoMold	-0.0478	-0.105 - 0.0129	0.107
	Fraction Number	0.000865	-0.000436 - 0.00217	0.193
LNG	MayoMold	-0.00556	-0.106 - 0.0925	0.909
	Fraction Number	0.0016011	0.000664 - 0.00257	0.00107
LAT	MayoMold	-0.0000652	-0.0486 - 0.0475	0.998
	Fraction Number	-0.000322	-0.00127 - 0.000635	0.508
RTN	MayoMold	0.238º	-0.0436º - 0.514º	0.0913
	Fraction Number	0.00193º	-0.00325º - 0.00694º	0.45579
Angle Alphas (α + α`)	MayoMold	1.260º	-0.024º - 2.511º	0.0516
	Fraction Number	0.0351º	0.00845º - 0.0615º	0.00854
Side Alpha	MayoMold	0.117	0.00200 - 0.234	0.0486
	Fraction Number	0.00242	0.000846 - 0.00403	0.00287
Side Gamma	MayoMold	-0.0143	-0.0552 - 0.0247	0.471
	Fraction Number	0.000232	-0.000273 - 0.000770	0.383
Side Alpha`	MayoMold	-0.0302	-0.128 - 0.0657	0.523
	Fraction Number	0.00156	0.000549 - 0.00256	0.00223
Side Gamma`	MayoMold	0.127	0.0103 - 0.244	0.0353
	Fraction Number	0.00131	-0.00000309 - 0.00263	0.0514

*A negative number in a “MayoMold” row implies the MayoMold cohort had a smaller mean difference from the DRR than the standard neck roll cohort did overall for that location and vice versa for a positive number.
A negative number in a “Fraction Number” row implies the MayoMold cohort had a smaller mean difference from the DRR than the standard neck roll cohort did when analyzed by treatment fraction number, which serves as a proxy for time progression, and vice versa for a positive number.
**BCI refers to a Bayesian Credible Interval.

Table 2: Systematic and Random Error in the MayoMold and Retrospective (standard neck roll) Groups

		Mean (cm)		Mean Difference (cm)	95% BCI (cm)
	Location	**MayoMold**	**Retrospective**		
Systematic Error	VRT	0.026	-0.0312	0.0574	-0.869 - 0.207
	LNG	0.0159	0.000607	0.0153	-0.157 - 0.185
	LAT	-0.0986	-0.0707	-0.0279	-0.159 - 0.0977
	RTN	0.241º	0.0996º	0.141º	-0.296º - 0.575º
	Angle Alphas (α + α\`)	-0.542º	1.21º	-1.75º	-4.94º - 1.35º
	Side Alpha	-0.124	0.0911	-0.215	-0.555 - 0.12
	Side Gamma	-0.0107	0.0135	-0.0242	-0.134 - 0.0875
	Side Alpha\`	-0.00476	-0.0261	0.0213	-0.214 - 0.252
	Side Gamma\`	-0.0707	0.0298	-0.1	-0.424 - 0.212
Random Error	VRT	0.165	0.161	0.00404	-0.0313 - 0.0409
	LNG	0.151	0.166	-0.0151	-0.0607 - 0.0298
	LAT	0.146	0.183	-0.0369	-0.0756 - 0.00197
	RTN	0.87º	0.588º	0.282º	-0.0388º - 0.602º
	Angle Alphas (α + α\`)	3.23º	1.65º	1.58º	-0.86º - 5.05º
	Side Alpha	0.282	0.268	0.0143	-0.0564 - 0.0849
	Side Gamma	0.0796	0.0925	-0.0129	-0.0317 - 0.00614
	Side Alpha\`	0.14	0.176	-0.0354	-0.111 - 0.0381
	Side Gamma\`	0.239	0.179	0.06	-0.0161 - 0.142