ISRRT Research Fund Application

PART I: SUMMARY OF RESEARCH PROPOSAL

1 (a) Project title: Quality Assurance of Image Registration for Adaptive Radiotherapy

1(b)   i). Primary Field: _____*Radiation Therapy*_____

Secondary Field: ___*Radiologic Technology*___

1(b)   ii). A maximum of five keywords to characterize the work of your proposal

Deformable image registration; dose accumulation; adaptive radiotherapy; quality assurance

2.   Investigator(s): (*Attach CV of each of the investigators*)

	Name (First name, Last name)	Email address	Affiliation	Address
Principal Investigator	Michael Velec	Michael.velec@rmp.uhn.ca	Radiation Medicine Program, Princess Margaret Cancer Centre	610 University Ave, Toronto, Ontario, Canada, M5G2M9
Co-investigator(s)	Tony Tadic	Tony.Tadic@rmp.uhn.ca	Radiation Medicine Program, Princess Margaret Cancer Centre	610 University Ave, Toronto, Ontario, Canada, M5G2M9
Co-investigator(s)	Vickie Kong	Vickie.Kong@rmp.uhn.ca	Radiation Medicine Program, Princess Margaret Cancer Centre	610 University Ave, Toronto, Ontario, Canada, M5G2M9

3.   Total Allocation Requested [in Pound Sterling]:   _£5,000_

4.   Duration of Project: __24__months

5.   Significance/Outcome of Project:

Deliverable 1: A validated scoring system for image registration quality with estimates of the associated dosimetric uncertainties in the lung, head and neck, and prostate sites.
Deliverable 2: Identification and evaluation of metrics that can be automatically computed and related to poor registrations for automatic, patient-specific quality assurance.

6.   Project proposal

i)   **Abstract of research** [**limited to ½ page or 250 words**, and comprehensible to a non-specialist]:

Adaptive radiotherapy strategies are being increasingly considered to account for unpredictable and complex patient motion occurring during image-guided delivery. Physiological motion and tissue responses from radiation may introduce uncertainties into the actual doses delivered. Deformable image registration between daily cone-beam CT and planning CT enables the impact of such motion on the doses delivered to patients to be estimated, a process termed dose reconstruction. This is a key component for adaptation, and therefore this process must be verified to ensure larger uncertainties are not introduced into treatment. Currently there is no established method to verify that the results based on deformable registration are accurate. The research proposal seeks to develop rapid and effective quality assurance methods for image registration. A preliminary scoring system has been developed for Radiation Therapists to perform simple visual assessments on routine image fusion. The first aim assesses the inter-rater reliability of the system and relates the qualitative scores to dosimetric uncertainties in treatment delivery. The second aim investigates automated methods to detect errors in the registration. Qualitative-based scores will be correlated to numerical image-based metrics that can be computed automatically and remotely. The sensitivity and specificity of a process to identify poor registrations on a patient-specific basis using the metrics identified will be evaluated. This research will enable efficient and effective quality assurance of deformable registration for dose reconstruction. This may facilitate the use of these tools by the community and enable safe implementation of adaptive radiotherapy strategies in the clinical setting.

ii)   **The project objectives and long-term impact** [**maximum 1 page**]: [*State the purpose of the proposed investigation, identify the key issues and problems being addressed, and state the possible outcome of the research project in terms of its relevance, significance and value. Please list in point form where appropriate*].

Purpose: To develop and evaluate methods for Radiation Therapists to perform quality assurance of image registration and fusion procedures relating to adaptive radiotherapy.

The key issues and problems addressed:
-    Errors in deformable registration and their related dosimetric errors require better understanding in order to prevent larger uncertainties from being introduced into treatment processes.
-    Guidelines to perform routine verification of deformable image registration between cone-beam CT and planning CT with the intended use of dose-tracking do not yet exist despite increasing interest in adaptive radiotherapy.
-    Radiation Therapists currently routinely perform verification of image registration for image-guided delivery, therefore it is reasonable to expect they will also be relied upon to perform deformable image registration verification in future adaptive techniques. Standardizing this process for Radiation Therapists will allow for evidence-based methods to be used throughout the community.
-    Workload and logistics are real barriers preventing adaptive strategies that have been developed in the research setting from being implemented in the clinic. The automated quality assurance methods developed in this proposal can potentially facilitate their uptake.

Relevance and significance:
- This proposal directly relates to the ISRRT's Mission Statement by developing standards and quality assurance methods for radiation therapy.
- As adaptive radiotherapy is an emerging paradigm, evidence-based guidelines are required to ensure new treatment techniques are safely applied to patients.
- There is a unique opportunity for this Radiation Therapy-led proposal to contribute quality assurance methods to radiation medicine.

Long-term impact:
- This research proposal is not intended to develop methods that are relevant to one institution or treatment planning system, but rather develop methods that can be widely adopted and applied by other institutions.
- Because clinical adaptive radiotherapy strategies are still in their infancy, this research is timely and proactively attempts to establish safe guidelines.
- The intention of this proposal is to develop practical methods that can be applied in the clinical setting and for planned clinical trials of adaptive radiotherapy at our institution and abroad.

iii) **Background/literature review of related work that has been done** [*maximum 2½ pages, including references*]:

Image-guided radiotherapy has revealed the dynamic nature of patients. Complex motion such as weight loss, breathing, organ filling and tumour responses are often visualized by Radiation Therapists when daily volumetric images such as cone-beam CT (CBCT) are fused to planning CTs. These sources of motion are difficult to correct online and often prevent the reduction of planning margins in an effort to spare more normal tissues from being irradiated. There is increasing interest is developing adaptive strategies to precisely account for this motion. More personalized therapy could further enhance therapeutic ratios and improve clinical outcomes.

Deformable image registration, a relatively recent addition to the clinical environment, is often use as a tool to facilitate adaptive radiotherapy in research studies[1]. It can be used to automatically propagate contours defined on the initial planning CT to subsequent re-planning CTs. In another more complex application called dose reconstruction (sometimes dose accumulation, or dose tracking), it is applied to CBCT images to track anatomy and motion at the voxel level. Dose to each voxel calculated on each CBCT is then mapped back to the planning CT and summed. These summed doses are then assumed to be an improved estimate of the 'true' dose delivered to the patient as they account for the motion observed on each CBCT. Retrospective studies have shown that delivered doses measured used dose reconstruction techniques differ from the planned dose distribution in the majority of patients, and normal tissue doses can differ as much as 40%[2]. The QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) consortia have called for robust and accurate dose reconstruction methods to improve our limited understanding of tissue dose-response models in additional to adaptive radiotherapy paradigms[3]. Two studies using deformable dosimeters demonstrated that dose reconstruction has the potential for large uncertainties if not applied properly, particularly in homogenous, low-contrast image regions (i.e. those often found on CBCT)[4,5]. Regardless, these fusion techniques are increasingly being incorporated into treatment planning systems and clinical processes, therefore, it is critical that the accuracy and behavior of these algorithms is well understood[6].

Our institution is currently transitioning to a new commercial treatment planning system with deformable image registration and capabilities to perform delivered dose reconstruction[7]. Eventually the intention is that this will additionally serve as a platform to develop and test adaptive radiotherapy. Our clinical team has recently commissioned the geometric accuracy

of the deformable image registration algorithms according to the newly released guidelines from the American Association of Physcists in Medicine (AAPM) Task Group 132 report[8]. The algorithms were validated in the thorax, abdomen and pelvis using diagnostic-quality imaging (e.g. CT, MR) for over 70 patients. The use of high-quality imaging instead of CBCT enabled registration accuracy to be quantified at organ boundaries and also internally using soft-tissue landmarks away from boundaries (e.g. vessel bifurcations inside the lung and liver). The latter features are generally not visible on CBCT imaging owing to the poorer soft-tissue contrast. Overall the algorithms performed with an accuracy on the order of the typical voxel size, typically 2-3 mm both at organ boundaries and within the organ volumes, within recommended tolerances[6].

For routine clinical application of CBCT-base dose reconstruction, however, such robust testing is neither practical nor feasible on a patient-specific basis. Quality assurance of image registration can be performed by visual verification to ensure that fusion performs similar to what was observed during commissioning. Radiation Therapists testing dose reconstruction in our department on a large numbers of patients have observed variable quality of image fusion between deformable image registration of CT and CBCT (Figure 1). For dose reconstruction and adaptive treatment strategies to be safe, the relationship between how the variable quality of registration affects the estimates of the delivered doses needs to be well characterized. Erroneous results from dose reconstruction (e.g. over or under estimation of the delivered doses) may trigger adaptive interventions such as re-planning for patient's that do not truly need it, or miss opportunities to re-plan and improve the therapeutic ratio in others. Samavati et al demonstrated that the geometric accuracy of image fusion may have a clinically significant impact on the decision-making metrics (i.e. dose-volume histograms) during delivered dose reconstruction for over 50% of patients[9]. Because CBCT quality makes quantification of fusion accuracy challenging, research is needed to link visual assessment of image fusion, paralleling clinical practice for standard image-guided radiotherapy, to dose reconstruction uncertainties.

Figure 1. Examples of CBCT deformed into the planning CT geometry. Solid lines show true organ borders defined on CT. Dashed lines show results of the deformable registration. Good results (left) means these lines overlap well. Poor results (right) used for dose reconstruction will cause errors in the delivered dose estimates.

There is currently a lack of evidence describing the accuracy of image fusion required for dose reconstruction beyond basic tests and tolerances for commissioning. Published guidelines from the AAPM explicit state that dose reconstruction is presently beyond of the scope of the Task Group report likely in part due to a lack of research in this area[8]. This gap in knowledge may limit the implementation of dose reconstruction and adaptive radiotherapy in the clinical setting. As Radiation Therapists are typically responsible for treatment planning dosimetry and performing image fusion for image-guided treatment delivery, there is a natural opportunity for Therapists to develop evidence-based guidelines on dose reconstruction for the community. This current proposal seeks to address these issues by developing and evaluating methods to enable routine quality assurance of CT to CBCT image fusion for adaptive radiotherapy.

References:

1. S Thörnqvist, LB Hysing, L Tuomikoski, A Vestergaard, K Tanderup, LP Muren, BJ Heijmen. Adaptive radiotherapy strategies for pelvic tumors - a systematic review of clinical implementations. *Acta Oncol* 55(8): 943-58 (2016).
2. M Velec, JL Moseley, T Craig, LA Dawson, KK Brock KK. Accumulated dose in liver stereotactic body radiotherapy: positioning, breathing, and deformation effects. *Int J Radiat Oncol Biol Phys* 15;83(4): 1132-40 (2012).
3. DA Jaffray, PE Lindsay, KK Brock, JO Deasy, WA Tomé. Accurate accumulation of dose for improved understanding of radiation effects in normal tissue. *Int J Radiat Oncol Biol Phys* 76(3)Suppl.1, S135-S139 (2010).
4. T Juang, S Das, J Adamovics, R Benning, M Oldham. On the need for comprehensive validation of deformable image registration, investigated with a novel 3-dimensional deformable dosimeter. *Int J Radiat Oncol Biol Phys* 87(2): 414-21 (2013).
5. M Velec, T Juang, JL Moseley, M Oldham, KK Brock KK. Utility and validation of biomechanical deformable image registration in low-contrast images. *Pract Radiat Oncol.* 5(4): e401-8 (2015).
6. M Velec, JL Moseley, S Svensson, B Hårdemark, DA Jaffray, KK Brock. Validation of biomechanical deformable image registration in the abdomen, thorax and pelvis in a commercial radiotherapy treatment planning system. *Med Phys.* Accepted for publication (2017).
7. O Weistrand, S Svensson. The ANACONDA algorithm for deformable image registration in radiotherapy. *Med Phys* 42, 40-53 (2015).
8. KK Brock, S Mutic, TR McNutt, H Li, ML Kessler. Use of image registration and fusion algorithms and techniques in radiotherapy: Report of the AAPM Radiation Therapy Committee Task Group No. 132. *Med Phys*, In Press. doi:10.1002/mp.12256
9. N Samavati, M Velec, KK Brock. Effect of deformable registration uncertainty on lung SBRT dose accumulation. *Med Phys* 43: 233–240 (2016).

iv) **Research plan and methodology** [*maximum 3 pages, including references*]:

Aim 1: Develop qualitative assessment method for quick image fusion verification

Initial data will consist of existing 20 cases each for the prostate, head and neck, and lung sites, with CT-CBCT deformable image registration performed on all fractions (i.e. ≥20 fractions) in the treatment planning system (RayStation v4.7, RaySearch Laboratories)[1,2]. Cases for current study will be selected to include a mix of registrations with low and high magnitude of deformation and with poor and excellent image fusions (as assessed visually). Based on published recommendations for image registration[3], we developed an initial scoring system to perform visual qualitative assessment of the image fusions intended to be used for dose accumulation (Table 1). Increasing uncertainty levels (ordinal, non-dichotomous) are scored based on the degree of visual misalignment of anatomical borders for relevant normal tissues and/or tumors if visible on CBCT.

Table 1 – Proposed scoring system

Score	Visual Assessment (to be refined in study)	Dosimetric Impact (to be quantified in study)
0	• All anatomy aligned within 2 mm	• Useful for dose accumulation everywhere • Dose uncertainty within expected variations
1	• Specific structures (e.g. controlling structures or high-contrast anatomy) for cumulative tracking aligned within 2 mm • Moderate misalignment (2–5 mm) elsewhere	• Useful for dose accumulation and evaluation of structures for tracking • Dose uncertainty to evaluation structures are within expected variations
2	• Specific structures for tracking aligned within 5 mm • Moderate misalignment (> 5 mm) of controlling ROIs or high-contrast anatomy • Gross misalignment (> 5 mm) of other anatomy	• Unusually large uncertainty in accumulated doses should be expected and reported • Mapped contours for grossly misaligned structures are erroneous without manual corrections
3	• Gross misalignment (> 5 mm) of specific structures (e.g. controlling structures or high-contrast anatomy) for dose evaluation structures • Unrealistic internal deformations	• Not suitable for dose accumulation • Mapped contours for grossly misaligned structures are erroneous without manual corrections

To evaluate the scoring system we will assess:

i) Inter-rater Reliability: Three observers (2 Radiation Therapists, 1 Medical Physicist) experienced in each anatomic site will score 10 cases (1 CT-CBCT fusion/case) for each anatomic site. Agreement between the raters will be assessed by means of the Fleiss kappa statistic. If the agreement is below fair (i.e. $\kappa < 0.40$) the observers will collectively review the descriptors in the scoring system and modify the definitions based on consensus, followed by another rater agreement test to confirm improved reliability. Results will be further confirmed by applying the scoring system to the remaining 10 cases as a validation cohort, and the full dataset on 3 new observers (2 Radiation Therapists, 1 Medical Physicist), for a total of 6 observers.

ii) Relationship to Dosimetric Uncertainty: The site-specific dosimetric impact of the quality of the image fusion on delivered dose reconstruction will be estimated. Radiation Therapists will score the fusions for all fractions for all 20 cases in each anatomic site. If <5 registrations exist per score additional patient data will be added. For each anatomic site, 20 image fusions for each of the 4 scores (each representing 1 treatment fraction) will be randomly selected and the dosimetric uncertainty will be quantified (80 measurement in total) as follows. Normal tissue contours from the planning CT will be propagated to the CBCT using the deformable image registration underlying the image fusion. Expert manual contours from experienced Radiation Therapists (assumed to represent the 'ground truth') will also be generated for the same structures directly on the CBCT. Differences between these contours represent the error in the underlying deformable registration. The delivered doses will be calculated on the CBCTs using existing functions in the planning system and relevant dose-volume histogram (DVH) metrics for the normal tissues will be computed. Mean, standard deviation, and range of the differences between DVH metrics based on manual versus propagated contours will be computed and represent the 'Dosimetric Impact' (Table 1). The strength and direction of association between the Visual Assessment Score and Dosimetric Impact will be graphed and quantified using Spearman's rank correlation coefficient (ρ). A positive and significant correlation ($P<0.5$) would indicate the visual scoring system may be useful for prospective image fusion quality assurance for dose reconstruction.

Deliverable of Aim 1: Validated scoring system with estimates of the associated dosimetric uncertainties in the lung, head and neck, and prostate sites.

Aim 2: Investigate techniques for automated quality assurance of image fusion

An in-house software platform (*MIRA*) has been developed, that integrates with the treatment planning system (RayStation) to automatically calculate and extract various

quantitative metrics relating to each CT-CBCT image registration available per patient. These metrics (e.g. change in volume for a specific organ, image similarity metrics etc.) can be reviewed using the web-based *MIRA* dashboard to visualize how they vary over the patient's treatment course (Fig 2). In practice, for metrics that relate to the quality of the image registrations, a large fluctuation in the metric value may indicate that a specific registration requires further investigation or intervention by a Radiation Therapist. The metrics investigated will be calculated on a region-specific basis (e.g. relevant normal tissues, volume encompassing the 95% isodose etc.) and will include:

- Image similarity metrics: correlation coefficient, mutual information
- Structure volume changes (e.g, lungs, bladder, tumors etc.)
- Descriptive statistics of the magnitude of the underlying deformation map (mean, standard deviation, 95th percentile, etc.)
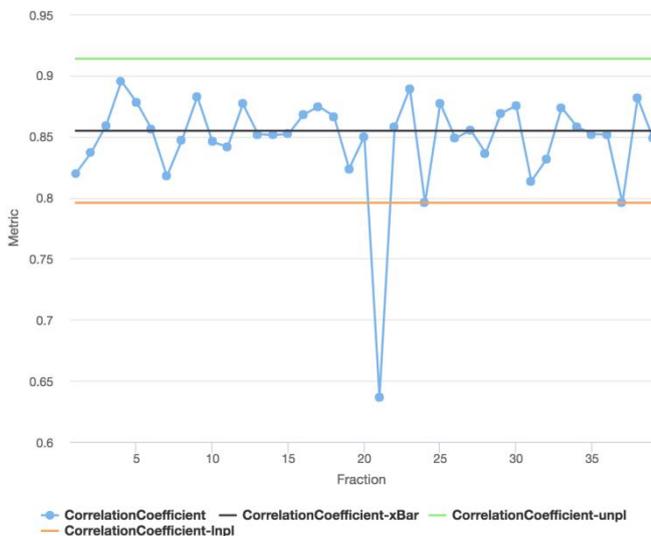

Fig 2: Example of a 'Shewhart' control chart generated by MIRA showing the correlation coefficient (CC) image similarity metric calculated and plotted for each fraction (mean = black line). Generally, CC is higher when CT-CBCT fusion has higher visual agreement. Statistically speaking, values exceeding the upper/lower natural process control limits (green/orange lines) indicate unexpected or unusual variation in the CC metric for this specific patient's image. The large spike at fraction 21, may represent a particularly poor image registration that would generate an erroneous result for dose reconstruction.

Image fusions for all fractions for 60 patients (20 per anatomic site) will be scored using the methods established in Aim 1. Metrics described above will be automatically calculated in RayStation and extracted by *MIRA*, and these will be correlated to the qualitative scores and dose uncertainties calculated in Aim 1 (Table 1). Spearman's coefficient (ρ) will be calculated to aid in evaluation of the candidate metrics. If a relationship can be identified, these metrics can potentially be used as an automated technique to perform quality assurance without the requirement for manual qualitative assessment in future patients. This would streamline dose reconstruction processes.

Using a technique termed statistical process control (SPC), *MIRA* calculates patient-specific control limits for each metric, to automatically indicate treatment fractions when unusual (i.e. out-of-control) values are encountered. Out-of-control signals for these metrics will be investigated for their relationship to changes in the qualitative scoring system. For example, if the registration worsens (e.g. a score of 3) for a patient from their baseline (i.e fraction 1, score of 1) SPC would be used to flag that fraction's registration. The sensitivity (true positive rate) and specificity (true negative rate) of fluctuations in the above metrics to detect poor registrations will be computed and compared. Metrics with the highest performance to detect poor registration may be used prospectively for automated quality assurance of image fusion.

Deliverable of Aim 2: Identify metrics that can be automatically computed and related to poor registrations for automatic, patient-specific quality assurance

References:

10. KK Brock, S Mutic, TR McNutt, H Li, ML Kessler. Use of image registration and fusion algorithms and techniques in radiotherapy: Report of the AAPM Radiation Therapy Committee Task Group No. 132. *Med Phys*, In Press. doi:10.1002/mp.12256
11. O Weistrand, S Svensson. The ANACONDA algorithm for deformable image registration in radiotherapy. *Med Phys* 42, 40-53 (2015).
12. M Velec, JL Moseley, S Svensson, B Hårdemark, DA Jaffray, KK Brock. Validation of biomechanical deformable image registration in the abdomen, thorax and pelvis in a commercial radiotherapy treatment planning system. *Med Phys.* Accepted for publication Author Manuscript.

v) **Working schedule** [Describe what will be done under "tasks" and shade the boxes to indicate when the task will be done]

Tasks	Year 1				Year 2			
	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter
Aim 1: Inter-rater reliability study	▓							
Aim 1: Refine scoring system		▓						
Aim 1: Validate scoring system		▓						
Aim 1: Contouring on CBCT		▓	▓	▓				
Aim 1: Relate scoring to doses				▓				
Aim 2: Perform scoring QA				▓	▓			
Aim 2: Extract metrics for MIRA						▓	▓	
Aim 2: Relate metrics to scores						▓	▓	
Aim 2: SPC analysis							▓	▓

7. i) Allocation requested:

Total cost of project:

Description of items	£
(a) Staff*	*4400*
(b) Equipment	*0*
(c) General expenses	*0*
(d) Conference (Max. £600)	*600*
Total amount requested :	£ *5,000*

ii) Justifications for allocation

*Allocation estimates are based on £1 = $1.77 (Canadian dollars, CAD)

Staff items describe the rate of a Research Associate to support the project by performing portions of the data collection and analyses. The Research Associate is a technical specialist in with expertise deformation image-registration analysis, coding and statistical analysis. The

institution-defined cost is £24/hr (inclusive of the hourly rate and benefit costs). This funding enables approximately 25 weeks of support at 0.2 full-time equivalent (FTE). The remaining activities required for this proposal are contributed by the study investigators (not funded by this application).

All other required equipment and general expenses, including computers and software licenses, already exists at the institution for this project.

8. **Supporting documents** [*List documents submitted in support of this application e.g. support letter for research from institution, ethics approval from Institute Review Board etc.*]

- Support letter from institution
- Approval from Research Ethics Board for retrospective data access (patient consent not required)

9. **Research ethics/safety approval**: [*The primary responsibility of seeking the relevant approval rests with the PI. If human subjects are involved in the research, the respective subject consent form together with the information sheet for subjects should be attached with this proposal.*]

Please check the appropriate boxes to confirm if approval for the respective ethics and/or safety issues is required.

		Approval not required	Approval obtained	Approval being sought
(i)	Human research ethics		☑	
(ii)	Ionizing radiation safety	☑		

10. **Declaration** [*Please check the appropriate boxes below and sign the form before submission.*]

☑ I declare that I have not received grant totaling to more than £20,000 in the past 12 months as a principal investigator.

☑ I confirm that none of the investigators are agents of for-profit, commercial company.

☑ I confirm that I have been a member of _the Canadian Association of Medical Radiation Technologists (CAMRT)_ (name of national radiography/radiological technology society) for not less than 2 years.

OR

❏ I confirm that I have been an associate member of the International Society of Radiographers and Radiological Technologists for at least 5 years.

Signature   : _____

Name   : ___Michael_____Velec____
                 (First name)   (Middle name)   (Last name)

Designation : _Radiation Therapist-Clinician Scientist_____

Institution   : _Princess Margaret Cancer Centre, University Health Network_

Date   : _April 30, 2017_____

Please submit electronically to: admin@isrrt.org

PART II INSTITUTIONAL ENDORSEMENT
[The PI's institution is required to complete this part to certify his/her status in the institution.]

1.a ☑ I confirm that the Principal Investigator _Michael Velec_ (name) has been a full-time

 Radiation Therapist-Clinician Scientist (position of Principal Investigator) of this

institution since _September 1, 2016_ (date).

OR

1.b ❑ I confirm that the Principal Investigator _____(name) will be a full-

time / part-time* _____(position of Principal Investigator) of this

institution starting _____(date).

2. Our institution (name of institution) _Princess Margaret Cancer Centre_ will fully support the
conduct of the proposed project if the application is successful.

Signature   : _____

Name   : _Brandee Pidgeon, BSc, MRT(T)_

Designation   : _Interim Manager of Clinical Operations, Radiation Therapy_

Institution   : _Princess Margaret Cancer Centre, University Health Network_

Date   : _April 27, 2017_____