Trials

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# Platform for the Evaluation of innovations in Radiation oncology through registry-based conduct of multi-centric pragmatic randomized trials: PERa implementation

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## Abstract

**Purpose** Radiotherapy has achieved substantial progress often attributed to accelerated technological innovation over decades. However, randomized controlled trials (RCTs) are costly, difficult to fund and to conduct, such that the generation of quality evidence is outpaced by changes in practice. We sought to evaluate the implementation performance of a platform approach to the conduct of pragmatic RCTs in radiation oncology.

**Methods** We implemented PERa, a platform consisting of a prospective registry of patients receiving standard-of-care radiation therapy, designed to support pragmatic registry-based RCT (rRCT) methods and staged informed consent. Implementation performance metrics included rate of registry enrollment, acceptability of re-contact and/or serving as controls for interventional trials, activation and recruitment of embedded comparative effectiveness rRCTs, compliance to study arms, and completeness of ePRO data acquired at scale.

**Results** Between January 1, 2018 and December 31, 2023, the registry accrued 1415 participants across 5 participating institutions. At time of stage 1 consent, 93% agreed to re-contact for participation in a clinical trial, and 97% consented to serve as control. Seven embedded rRCTs were activated, and one third of participants ($n=477$) were randomized. Only two study arm non-compliance events were recorded. Although 97% of subjects consented to ePROs, completion rate was only 53% in those with stage 1 only consent, rising to 62% in those subjects also consented at a second stage to a companion rRCT.

**Conclusion** The PERa platform is met with high acceptance demonstrating efficient conduct of rRCTs embedded in routine radiation oncology practice. Future work to improve ePRO completions and automate harmonization with EMR data lakes have the potential to improve the quality of evidence generation and support learning health systems.

**Trial registration** NCT03378856: Registered on December 12, 2017. NCT04100174: Registered on September 20, 2019. NCT04178174: Registered on November 17, 2019. NCT05457699: Registered on July 04, 2022. NCT04405401: Registered on May 24, 2020. NCT04901234: Registered on May 17, 2021. NCT05317026: Registered on March 08, 2022.

**Keywords** Radiation oncology, Oncology, Pragmatic trials, Clinical trials, Patient-reported outcomes, Randomized controlled trials, Registry, Trials within Cohorts

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## Background

Randomized controlled trials (RCTs) remain the gold standard for measuring the impact of new therapeutic interventions. However, there are several limitations to the conduct and interpretation of conventional RCTs in radiation oncology, including high costs related to monitoring and follow-up, challenges with consent and recruitment leading to slow or ineffective accrual, as well as limited generalizability owing to stringent selection criteria [1], such that insufficient trials are being run to evaluate new technologies or treatment strategies [2].

Absence of quality evidence can lead to slow and unequal adoption of beneficial novel approaches, as well as lack of reimbursement by public or private insurers. Conversely, a new technology can be adopted early without high level evidence, and later be found to be ineffective or even harmful, so-called medical reversal [3]. The conduct of high-quality RCTs is thus desirable, and novel trial methods are needed to overcome current challenges with trial design.

In oncology, approaches to streamline trial conduct include the multi-arm multi-stage (MAMS) design of the STAMPEDE trial, which has randomized 11,992 patients since 2005, with multiple important findings having been reported in the last 10 years [4]. Large observational cohort studies serving to conduct interventional trials have also been deployed in colorectal cancer [5] and others. Another reported approach has focused on better trial integration in clinical care and use of integrated consent, as in the REaCT program [6]. This approach has proven effective to run trials comparing different standard of care (SOC) interventions.

Here we postulate that a collaborative platform based on systematic collection of high-quality clinical data and patient-reported outcomes from daily radiotherapy practice across institutions would drive the conduct of registry-based RCTs (rRCTs) and impactful research in radiation oncology.

## Methods

### Platform design and staged consent model

Platform for the Evaluation of innovations in Radiation oncology (PERa) was conceived as a prospective observational registry of consenting participants enrolled during a standard of care (SOC) visit in the radiation oncology department. The structure was designed to support the conduct of rRCTs, including conventional pragmatic RCTs, but also cohort multiple randomized controlled trial (cmRCT) methods [7] (also known as Trials within Cohorts (TwiCs) [8]. Although observational research from the prospective registry was supported, companion comparative effectiveness rRCTs were prioritized in the design build and rollout. The cohort thus served as a real-world pool from which eligible subjects could be screened, selected, and enrolled in an interventional rRCT.

A key feature of the PERa design is that the opt-in informed consent process was structured to mirror the informed consent procedures of usual care where possible. This approach was selected to reduce decisional burden information overload that can occur when patients are simultaneously making decisions about care and participation in an interventional clinical trial. We also strove to lessen the cost and burden on clinical and research staff by simplifying consent procedures for the observational (or control) cohorts.

In a first stage, patients are asked to provide broad upfront consent for use of their clinical data for the purposes of research. Optionally, they may also consent to any/all of the following:

a) Completing periodic health questionnaires (ePROs), optionally via emailed web link
b) Agree to be re-contacted to be offered an experimental intervention if deemed eligible (required for all rRCTs), which may include the eligibility criterion of having been selected by chance (required for cmRCTs)
c) Agree for data to be used as a control for comparison against subjects receiving an experimental intervention in a trial context without being notified (required for cmRCTs)

At PERa enrollment, patients consenting to (b) are screened for eligibility to any actively accruing companion rRCTs. If they are eligible for a cmRCT and have consented to (c), randomization proceeds and only those patients randomly selected for the experimental intervention are approached for second-stage consent specific to the experimental intervention. If they are eligible for a conventional rRCT, all eligible patients are re-contacted and approached for study enrollment in a second stage of consent prior to randomization. Figure 1 illustrates this process. All randomizations are 1:1 utilizing a variable block randomization model, with/without stratification based on the specific trial design. Blinding is therefore only possible for conventional RCTs within the platform.

The cmRCT approach has been proposed as a more streamlined and efficient way of obtaining consent, particularly in the context of pragmatic clinical trials where usual care is well established and consistent over time, and investigational interventions are costly, highly desirable, and difficult to access [7]. Thus (as is the case in usual care) only patients who have access to an investigational intervention being evaluated are actually given

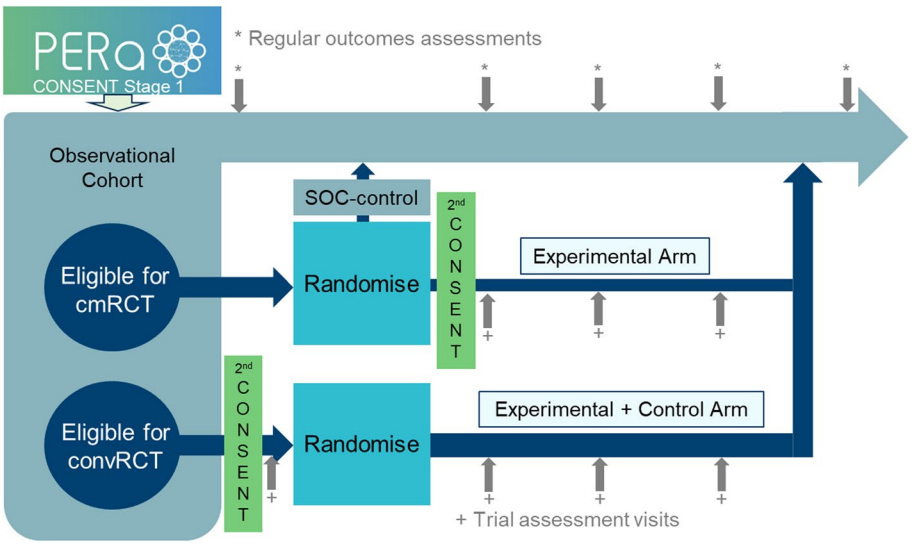


**Fig. 1** PERa design and staged consent model. Participants provide a consent at stage 1 and are enrolled in a SOC observational cohort with regular outcome assessment. Participants meeting embedded trial eligibility are identified and approached for a second-stage consent before (conventional RCT) or after (cmRCT-TwiCs) randomization. Only those patients separately consented to an embedded trial may undergo trial assessment visits beyond regular outcome assessment, if needed. Patients eligible for a cmRCT that are randomized to the control arm are returned to the SOC registry group for follow-up. cmRCT: cohort multiple randomized controlled trial, convRCT: conventional RCT, SOC: standard of care

information about that option [9, 10]. Patients assigned to a standard-of-care arm do not proceed to a second-stage consent where this information is provided.

However, for instances where usual care varies and there is equipoise in multiple usual care practices, conventional RCT methodology and consent modalities are favored. This also applies to instances where trial-specific endpoint metrics or additional screening investigations are not routinely captured in regular assessments.

The above framework was first submitted and approved by the sponsor site Ethics Review Board, and later at each participating institution with local adaptations. PERa is housed on a web-based electronic data capture system (castoredc.com), where study data is saved in real-time and stored on a certified and compliant server. The cyberstructure of electronic case report forms (eCRFs) are tailored according to oncological site groups (prostate, head and neck, lung, gastrointestinal, symptom control, sarcoma, and breast) based on their respective research objectives.

After consenting to participation in the registry (verbal to be followed by hard-copy signed ICF), subjects are registered by research staff with entry of consenting data, baseline demographic information, and site group designation. Staff are then instructed to send site-group specific survey packages to patients (ePROs) and treating physicians (or their designate) by emailed weblink for capture of baseline clinical data. Once baseline data entry is completed, research staff verify eligibility to actively accruing rRCTs, and proceed to pre- or post-randomization second-stage consent as detailed above.

Subsequent data entry for outcome assessments varied, with some site groups electing for automated physician surveys, while other sites relied on limited manual eCRF data entry from the electronic medical record (EMR) by research staff. In order to enhance safety of data capture for randomized subjects, routine reports of hospital admissions, emergency room visits, or surgical procedures captured within institutional data lakes were provided to the study team and events investigated to determine if they constituted recordable adverse events (AE).

## Funding structure

Start-up institutional and small industry seed funding was obtained to support platform implementation costs at the sponsor site. Each participating institution then locally assumed the cost of PERa site operations. In order to secure the sustainability of the PERa platform, principal investigators were encouraged to obtain grant funding for rRCTs or specific prospective registry projects including minimal overhead for use and support of PERa infrastructure.

## Implementation assessments

De-identified data was exported and analyzed using R [11] to evaluate the following metrics: rate of registry enrollment, acceptability of re-contact and/or serving as

controls for interventional trials, activation and recruitment of embedded comparative effectiveness rRCTs, compliance to study arms, and completeness of ePRO data acquired at scale. ePRO completion rates were compared using a chi-square test to obtain $p$ values.

## Results

### Stage 1 consent—implementation outcomes

PERa was activated in September 2017 in a limited run-in phase at the sponsor site, and broadly activated for patients with prostate cancer in concert with the activation of the first rRCT (PSMAgRT-NCT03525288) on April 5, 2018. Other participating sites were activated on November 12, 2019 (for rRCT participation), December 2, 2022 (for rRCT participation), February 21, 2022, and April 19, 2023, for registry enrollment alone at the time of data analysis. The first two sites funded their participation through rRCT-related funding, while the later two secured local institutional funding for registry-only participation.

At data analysis cutoff on December 31, 2023, PERa had enrolled 1415 subjects (Fig. 2a and b). Recruitment has been steady, with the first 500 patients enrolled over 710 days after excluding the run-in period from September 2017 to January 1, 2018. The next 500 subjects were recruited over 993 days, and the last 418 subjects over 396 days.

We found high acceptability of the PERa model as a platform for the conduct of rRCTs as demonstrated by responses to optional consent questions. The acceptance rate for their data being used as a control against subjects receiving an experimental intervention was 97%, while 93% agreed to be re-contacted if deemed eligible for an interventional trial.

### Stage 2 rRCT consent—implementation outcomes

Seven rRCTs were activated across oncological site groups, to date all initiated from the PERa sponsor site (Table 1). Four were deemed suitable for cmRCT methods and pre-randomization prior to second-stage

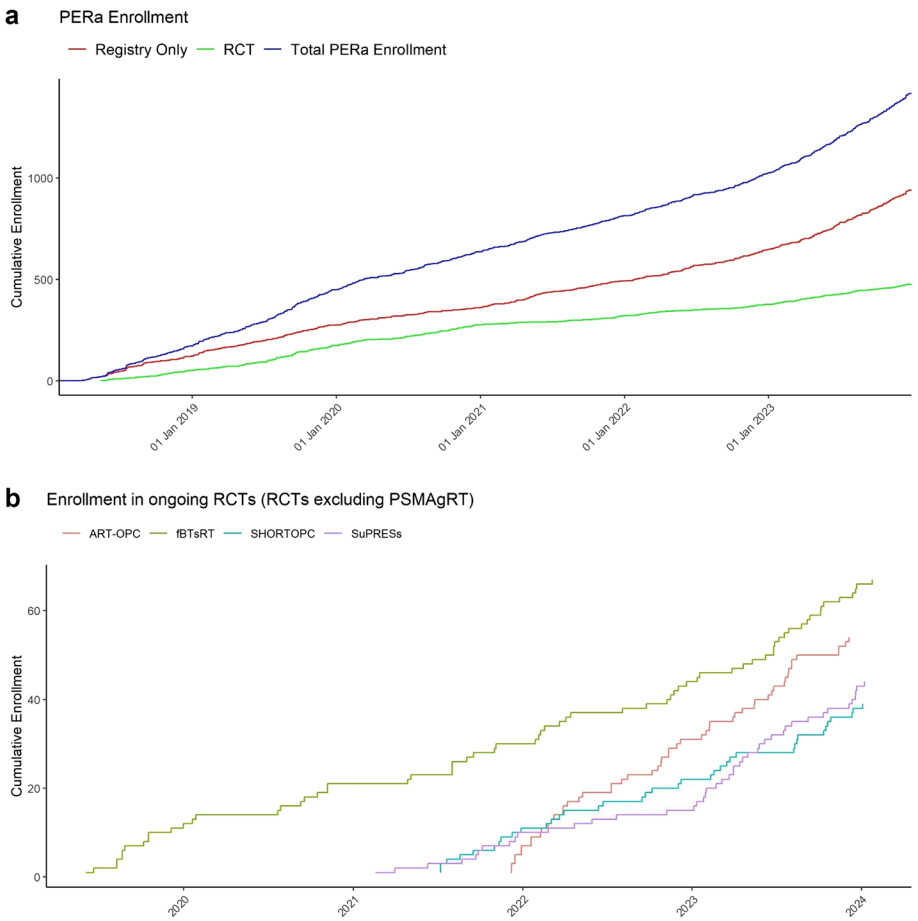


**Fig. 2** **a** PERa enrollment over time. **b** Enrollment in ongoing RCTs. Top—cumulative enrollment in PERa (blue), showing the number randomized in rRCT (green) and those included in the registry only (red). Run-in period prior to January 1, 2018, was censored. Date of activation of partner sites is also shown. Bottom—enrollment in rRCTs over time

**Table 1** Summary of embedded rRCTs in PERa (accrual updated to Aug 2024)

| Trial NCT | Site group | Institution | Intervention (primary endpoint) | Rando. method | Activation date | Status Accrual |
|---|---|---|---|---|---|---|
| PSMAgRT 03525288 | Prostate | CHUM, CSSL | PSMA-PET guided iRT (5 y FFS) | Pre-consent stage 2 | Apr 4, 2018 | Active, ongoing analysis $n=262/262$ |
| fBTsRT 04100174 | Prostate | CHUM, CHUQ | Focal HDR brachytherapy boost to stereotactic radiotherapy (urinary QoL) | Pre-consent stage 2 | Apr 8, 2019 | Active, enrolling $n=92/150$ |
| SuPRESs 04405401 | Multi-site | CHUM | SABR to oligoprog. lesions (PFS) | Post-consent stage 2 | Oct 29, 2020 | Active, enrolling $n=61/136$ |
| ART-OPC 04901234 | Head and neck | CHUM | Mid-treatment MR-guided RT adaptation (dysphagia) | Post-consent stage 2 | Nov 12, 2021 | Active, enrolling $n=62/120$ |
| SHORTOPC 04178174 | Head and neck | CHUM | SABR boost + de-escalated RT (locoregional control) | Post-consent stage 2 | Feb 14, 2020 | Active, enrolling $n=44/106$ |
| ANCHOR 05457699 | Prostate | CHUM | SABR consolidation (1 y FFS) | Pre-consent stage 2 | Nov 18, 2022 | Active, enrolling $n=1/80$ |
| V-SBRT 05317026 | Symptom control | CHUM | Vertebroplasty prior to SBRT (pain) | Pre-consent stage 2 | Dec 13, 2022 | Active, enrolling $n=4/50$ |

*PSMA-PET* Prostate-Specific Membrane Antigen Positron Emission Tomography, *iRT* Intensified Radiation Therapy, *HDR* High-Dose Rate, *SABR* Stereotactic Ablative Radiotherapy, *RT* Radiation Therapy, *SBRT* Stereotactic Body Radiation Therapy

consent, and 3 rRCTs were better suited to randomization post second-stage consent due to variations in standard of care practice. Although only two rRCTs were multi-institutional, efforts are ongoing to expand activation of the remaining rRCTs to other partner sites.

The first rRCT successfully enrolled 262 patients across two institutions, closing to accrual in February 2021 [12, 13]. In contrast, the most recent rRCTs have been slower to accrue (Table 1) and mitigating strategies to increase accrual are being implemented. Overall, a third of subjects were randomized to an embedded rRCT within PERa (Fig. 3).

Compliance to the study arm assignment is essential to the validity of trial findings, but can prove more challenging with a cmRCT and/or pragmatic design. Within PERa, study arm compliance was high, with only one non-compliance event identified for the PSMAgRT trial (one patient selected for the experimental intervention refusing), and one withdrawal of consent for the ART-OPC trial. For other active RCTs, there have so far been no such events identified.

### ePRO completion performance

We analyzed the ePRO completion for patients recruited while PSMAgRT was active (May 2018 to February 2021). At stage 1 consent, 97% of subjects approached consented to ePROs. Of 2855 surveys automatically sent by email at the time of the last data update, 1633 (57%) had been completed by patients. The rate was higher in patients in the experimental arm of PSMAgRT (i.e., consented to stage 2) at 69% compared to subjects only consented at stage 1 (53%). We also observed higher completion rates for all RCT experimental arms when compared to control arms (Table 2, $p=0.005$), regardless of whether the RCT was conventional or a cmRCT. For subjects with stage 2 consent, which includes subjects in the experimental arm of cmRCTs and both experimental and control arms of conventional RCTs, the completion rate was 62%. Implementation of external monitoring in the fBTsRT trial considerably improved ePRO completion rates (83% control, 90% experimental).

## Discussion

Implementation of the PERa platform has been met with high acceptance demonstrating efficient conduct of rRCTs embedded in routine radiation oncology practice. By combining systematic collection of clinical data and patient-reported outcomes from daily radiotherapy practice with a streamlined two-stage consent model, we successfully conducted a large phase 2 rRCT evaluating PSMA-guided intensification of radiation therapy in prostate cancer. Early outcomes from this trial have since led to the funding and recruitment of a confirmatory phase 3 RCT [14], demonstrating the potential value of the proposed approach to impact care.

Building on the successes of this trial, PERa activated six subsequent companion RCTs while also expanding the registry beyond the sponsor site to four centers in Canada, two of which have actively recruited into companion rRCTs.

Importantly, we have not observed potential non-uptake of experimental intervention arm with pre-randomization for those trials designed per TwiCs. This may be due to stringent selection of the most

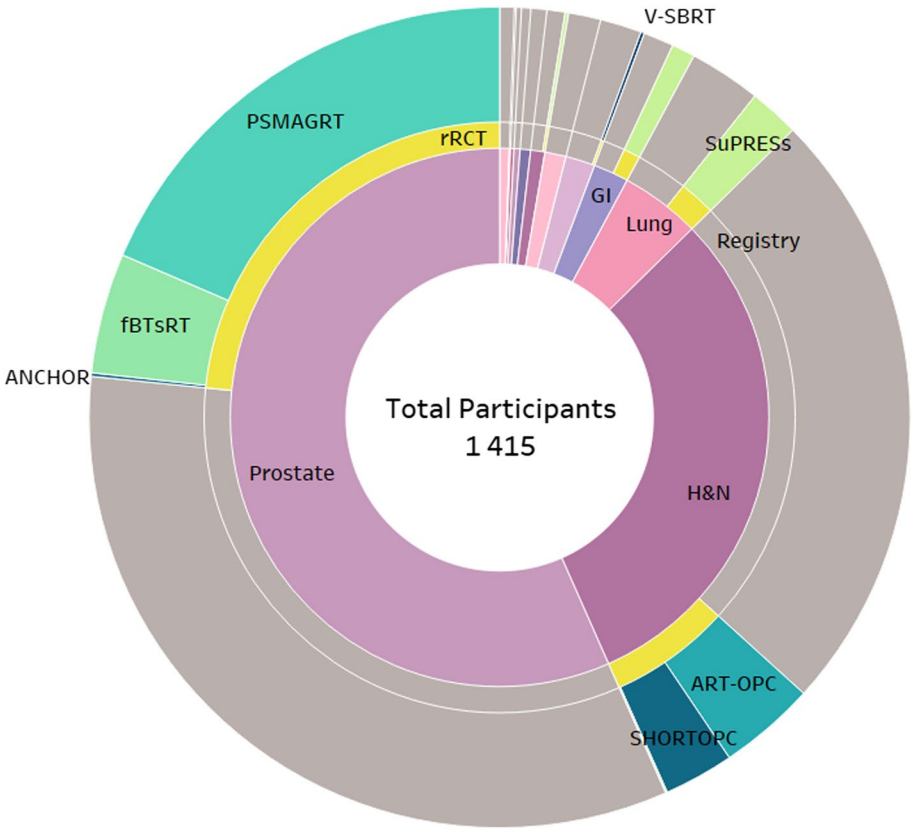


**Fig. 3** Distribution of PERa participants. The inner ring represents the site group, randomized in the yellow center ring, and the related rRCT in the outer ring. Registry-only subjects are in gray. H&N: head and neck, rRCT: registry RCT, GI: gastrointestinal

**Table 2** ePRO completion rates in RCTs and a registry comparator

| Trial | % Completed in Experimental Arm | % Completed in Control Arm | *p*-value |
|---|---|---|---|
| All RCTs | 67% | 56% | 0.0052 |
| ART-OPC | 59% | 51% | 0.19 |
| fBTsRT | 90% | 83% | 0.077 |
| PSMAgRT | 69% | 54% | 0.00035 |
| SHORTOPC | 58% | 51% | 0.36 |
| SuPRESs | 68% | 56% | 0.06 |
| | % Completed | *p*-value vs PSMAgRT Experimental Arm | *p*-value vs PSMAgRT Control Arm |
| Registry Comparator | 53% | $2.184\times10^{-11}$ | 0.7172 |

*P*-values computed using Pearson's chi-square method

*RCT* Randomized Controlled Trial

suitable trials for this approach which is especially suited to clinical research areas characterized by rapid evolution of technology, and for highly accepted or expensive interventions that are not yet widely available in the health care system. As this is not a fits-all methodology, it was important to enable more conventional post-consent randomization for other less suited trials. This also allows the platform to accommodate more or less pragmatic RCTs, depending on the study question. Despite these successes, a number of challenges remain.

We did observe non-equal completion rates of ePROs between the experimental and control arms of RCTs. This may be due to patients approached for a second-stage consent being reminded of their participation in research, the experimental nature of their treatment, and consequently more compliance in completing ePROs. It may also stem from well-meaning research staff who focused more on subjects providing a second-stage consent for prompting ePRO completion beyond automated email sends. By highlighting this discrepancy, efforts have since included additional training of research staff to prompt and support all randomized subjects (both control and experimental) equally for ePRO completion. This step is of highest relevance for trials in which the primary endpoint relies on ePROs, where the use of external monitoring (fBTsRT) has also led to higher rates

of completion. In the hopes of facilitating ePRO completion in the future, ethics approval has been obtained to implement use of an app for personal devices. Permitting patients to use their own device and having a range of options for ePRO completion may improve completion rates. Informing patients randomized to the standard-of-care arm that they are being included in a prospective study could also be explored as a way to improve adherence.

Limitations of the design include the reliance on busy clinicians or their staff to enroll patients onto the registry. Computational methods to systematically offer participation to all eligible subjects, including electronic consent, are of high relevance in this context and are actively being pursued.

Finally, although the platform has been expanded to additional partner sites beyond the sponsor institution, the current activity remains heavily centralized. It is imperative to decentralize rRCT sponsorship by other centers in order to improve trial result generalizability. To this end, the legal and ethics structure has been simplified to lessen initial burden of activation, and to permit partner centers to lead and sponsor future rRCTs within PERa. A clear governance structure has reassured partner sites who control their own institutional data with an explicit data sharing procedure. Sustainable funding of the platform also remains a challenge. To that end, we plan to explore philanthropic strategies, in addition to government, institutional, and industry partner support.

### Future directions and exploratory endpoints

Currently, we have planned an analysis that includes the use of administrative data to improve the capture of clinically relevant endpoints. In this case, an exploratory project explored data mining to identify adverse events not captured by the registry; this will be reported in a future publication.

Future work to automate harmonization with EMR data lakes and methods to improve ePRO engagement of enrolled subjects have the potential to improve the quality of evidence generation within PERa. With the upcoming broad implementation of adaptive radiotherapy enabled by newly deployed technologies, we are poised to better measure the clinical impact of such a promising technological innovation. In a further step, engagement in ePROs could also be harnessed to enroll in future symptom-intervention trials [15].

## Conclusion

We showed that a registry-based RCT platform is feasible in current radiation oncology practice. By generating high-quality evidence from RCTs, it has the potential to contribute to the establishment of learning health systems and improved patient outcomes.

**Abbreviations**

| | |
|---|---|
| PERa | Partnership for the Evaluation of innovations in Radiation oncology |
| RCTs | Randomized controlled trials |
| rRCT | Registry-based randomized controlled trial |
| cmRCT | Cohort multiple randomized controlled trial |
| TwiCs | Trials within Cohorts |
| ePRO | Electronic patient-reported outcomes |
| MAMS | Multi-arm multi-stage |
| SOC | Standard of care |
| eCRF | Electronic case report forms |
| EMR | Electronic medical record |
| AE | Adverse events |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-026-09709-0.

Supplementary Material 1.

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**Authors' contributions**
Philippe Giguère: conceptualization, data curation, writing—original draft, review and editing, visualization, project administration. Cynthia Ménard: conceptualization, methodology, investigation, writing—original draft, review and editing, supervision. Houda Bahig: conceptualization, investigation, review and editing. Sydney Westra: data curation and visualization. Others: writing—review and editing, investigation.

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**Data availability**
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
The PERa registry and embedded clinical trials underwent review by institutional Ethics Review Boards. All registry and participants provided written informed consent.

**Consent for publication**
Not applicable.

**Competing interests**
Houda Bahig—research grant from Varian Medical Systems and AstraZeneca. Advisory boards and speaker fee from AstraZeneca and EMD Serono. Cynthia Menard—research grants from Varian Medical Systems, Promaxo, Tersera, and Lantheus. All other authors declare no relevant potential competing interests.

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## Publisher's Note