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## CRITICAL REVIEW

# Framework for Quality Assurance of Ultrahigh Dose Rate Clinical Trials Investigating FLASH Effects and Current Technology Gaps



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**Abstract:** FLASH radiation therapy (FLASH-RT), delivered with ultrahigh dose rate (UHDR), may allow patients to be treated with less normal tissue toxicity for a given tumor dose compared with currently used conventional dose rate. Clinical trials are being carried out and are needed to test whether this improved therapeutic ratio can be achieved clinically. During the clinical trials, quality assurance and credentialing of equipment and participating sites, particularly pertaining to UHDR-specific aspects, will be crucial for the validity of the outcomes of such trials. This report represents an initial framework proposed by the NRG Oncology Center for Innovation in Radiation Oncology FLASH working group on quality assurance of potential UHDR clinical trials and reviews current technology gaps to overcome. An important but separate consideration is the appropriate design of trials to most effectively answer clinical and scientific questions about FLASH. This paper begins with an overview of UHDR RT delivery methods. UHDR beam delivery parameters are then covered, with a focus on electron and proton modalities. The definition and control of safe UHDR beam delivery and current and needed dosimetry technologies are reviewed and discussed. System and site credentialing for large, multi-institution trials are reviewed. Quality assurance is then discussed, and new requirements are presented for treatment system standard analysis, patient positioning, and treatment planning. The tables and figures in this paper are meant to serve as reference points as we move toward FLASH-RT clinical trial performance. Some major questions regarding FLASH-RT are discussed, and next steps in this field are proposed. FLASH-RT has potential but is associated with significant risks and complexities. We need to redefine optimization to focus not only on the dose but also on the dose rate in a manner that is robust and understandable and that can be prescribed, validated, and confirmed in real time. Robust patient safety systems and access to treatment data will be critical as FLASH-RT moves into the clinical trials. © 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

## Introduction

In 2014, Favaudon et al<sup>1</sup> introduced FLASH radiation therapy (FLASH-RT), an ultrahigh dose rate (UHDR) technique that spared normal tissues without compromising antitumor efficacy in mice compared with conventional dose-rate irradiation. Their publication ignited strong interest in the RT community, and subsequent preclinical *in vivo* studies similarly demonstrated improved therapeutic index using UHDR electron, proton, and photon beams.<sup>1-17</sup> In recent years, with the increase in cancer survivors' life expectancies, concern about potential radiation-induced toxicity has increased. FLASH-RT potentially enables the reduction of normal tissue toxicity with a standard tumor dose or the maintenance of comparable toxicity with an increased effective tumor dose.<sup>18-22</sup> Furthermore, its ultrarapid treatment delivery minimizes motion impacts. The performance of clinical trials of FLASH-RT examining normal tissue

protection, tumor lethality, and UHDR treatment deliverability and definitions is the primary goal of the translation of preclinical research.

Clinical trials of FLASH-RT conducted with animals (eg, cats and pigs) recently revealed late toxic effects.<sup>23</sup> The FAST-01 trial (ClinicalTrials.gov identifier: NCT04592887) demonstrated the feasibility of proton FLASH-RT for humans with multiple bone metastases.<sup>24,25</sup> The FAST-02 trial, designed to examine proton FLASH-RT for bone metastases in the chest, is now open for enrollment. A clinical trial examining electron FLASH-RT dose escalation for human patients with skin melanoma metastases (ClinicalTrials.gov identifier: NCT04986696) was initiated in 2021. Ongoing and planned clinical trials of FLASH-RT are designed to test the UHDR deliverability and safety with the examination of the effectiveness of tumor control, normal tissue dose tolerance, the reproducibility of treatment effects across multiple institutions, and the safety and effectiveness

of combined chemoradiation treatment paradigms. The success of planned FLASH clinical trials examining these and other hypotheses is contingent on the consistency and quality of UHDR technology implementation and reporting.

Presently, it is unclear what parameters of UHDR RT (including potential dose and/or dose rate thresholds) are required or optimal to produce FLASH effects. In early publications, 40 Gy/s was suggested as a dose-rate threshold.<sup>1,2</sup> Subsequent studies have demonstrated that the dose, intrapulse dose rate, and number of pulses play important roles in electron FLASH effects.<sup>26-28</sup> Although *in vivo* animal FLASH studies have been performed with single scattered and collimated beams, clinical particle-beam UHDR treatment delivery used and likely will use pencil beam scanning (PBS) that employs lateral scanning of a series of pencil beams located at various depths to cover the tumor volume. Use of the plateau region of transmission beams<sup>29,30</sup> or range modulation with the use of specific accessories<sup>31,32</sup> were proposed to preserve the PBS-specific UHDR.<sup>29,30,33,34</sup>

Only when details in UHDR dose and dose-rate parameters are available can the effects of clinical trial protocols on patients be systematically evaluated. The clinical trial treatment planning must consider beam delivery time structures to optimize UHDR dose distributions. Planning evaluation and reporting tools, such as voxel-based dose delivery time structure and knowledge of the UHDR beam parameters, are essential for the conduct of meaningful clinical trial studies, study reproducibility, and translatability<sup>35</sup> and will facilitate the inclusion of these parameters for optimal UHDR implementation.<sup>36</sup> Note that the UHDR parameters needed for optimal FLASH effects would most appropriately be determined through preclinical and clinical trials rather than specified as quality assurance (QA) metrics. However, the ability to document critical parameters accurately would fall under clinical trial credentialing.

Other critical requirements for FLASH-RT clinical trials are robust dosimetry methods, techniques, and equipment that enable the reliable and reproducible measurements of doses and dose rates. Traditional dosimetry tools need to be validated for the recording of doses under UHDR conditions. A new series of dosimetry systems need to be developed and validated for the recording of dose delivery timing information at sufficient resolution. In addition, the safety and repeatability of UHDR dose delivery within and across institutions must be demonstrated, at least for the same modality.

The NRG Oncology Center for Innovation in Radiation Oncology formed a FLASH working group (NCFWG) with physicists and physicians from multiple institutions with the experience and intention to implement UHDR FLASH-RT. This report is based on the current team consensus regarding the framework on QA and credentialing of potential FLASH clinical trials and the technology status and challenges. It should not be referred in regular clinical practice. It addresses the following topics specific to electron and proton UHDR clinical trials: requirements for treatment delivery reports, the definition and control of safe UHDR delivery, dosimetry requirements, recommendations for treatment plan reporting,

and requirements for FLASH-RT system credentialing and QA. The recommended percentage uncertainties and thresholds are preliminary and should not be used as a basis for regulatory specifications. We conclude this report with a summary of the current state of technology and technological gaps relevant to future NRG FLASH-RT clinical trials.

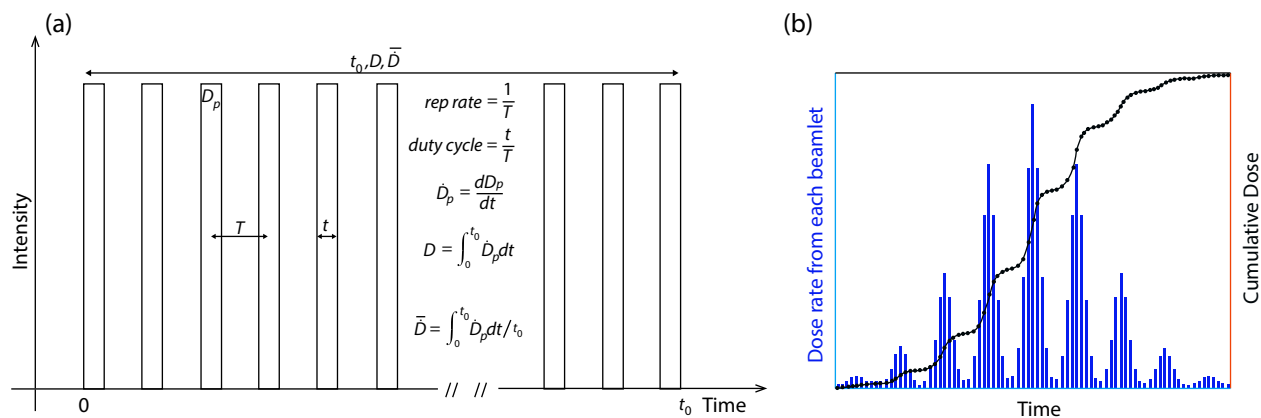
## FLASH-RT Delivery Reports

Various UHDR delivery technologies have been explored and invented given the rapidly evolving nature of FLASH-RT research. Preclinical studies have been made possible with the development of dedicated experimental systems and modification of existing RT systems,<sup>37</sup> including specialized electron linear accelerators (LINACs),<sup>1,38</sup> proton/particle beam-lines,<sup>6,39-42</sup> synchrotron light sources producing kilovoltage x-rays,<sup>43</sup> small animal irradiators with customized kilovoltage x-ray tubes,<sup>44,45</sup> and the conversion of clinical LINACs.<sup>46-49</sup> Newly designed systems with the main function of UHDR-RT<sup>50</sup> include the PHASER platform,<sup>51</sup> electron FLASH system for intraoperative RT,<sup>52,53</sup> and external beam RT with very-high-energy electrons.<sup>54,55</sup> Current translational studies and pilot human clinical trials have been conducted predominantly with UHDR electron and proton beams within conventional clinical therapeutic energy ranges.<sup>24,38,56</sup> Here, to provide recommendations on reportable beam parameters for FLASH clinical trials that are ongoing and planned for the foreseeable future, the scope of the discussion is limited to UHDR-RT with electron and proton beams at energies used in current clinical practice; the considerations and recommendations may or may not apply to other modalities such as heavy-ion and photon UHDR-RT.

The NCFWG has reached the consensus that all reportable beam parameters for current clinical treatment with conventional dose rates for electron RT and proton therapy, preferably with definitions and measurement conditions specified in established professional guidelines, remain applicable to UHDR-RT. These parameters include (1) the treatment regimens, geometries, dose distributions, energies, percentage depth doses, output factors, and lateral profiles for a range of field sizes for electron beams, and (2) the treatment regimens, geometries, dose distributions, energies, linear energy transfer, spot profiles (for pencil beam) or lateral profiles (for scattered beam), integral depth doses (for pencil beam) or percentage depth doses (for scattered beam), and output factors/halo effects for various field sizes and range modulations (eg, spread-out Bragg peaks) for proton beams. Beam parameters of particular interest for electron and proton UHDR-RT are summarized here, with discussion and recommendations for delivery reports.

## Electron beam therapy

Studies involving the use of UHDR electron beams, implemented primarily with specialized irradiators and modified



**Fig. 1.** (a) Schematic of electron temporal pulse structures of extracted beams with key parameters defined. (b) Dose rates and cumulative doses from each spot on a square field of proton pencil beam scanning delivery to the Bragg peak (central axis). The spots are of the same intensity and energy and are uniformly spaced. See [Table 1](#) for variable definitions.

medical LINACs, have revealed significant variation in the pulse structure (instantaneous dose rate, dose per pulse, pulse width/duration, pulse repetition frequency, and mean dose rate).<sup>1,46,48,52,53,57-59</sup> To facilitate the cross-platform interpretation of outcomes and reproducibility of irradiation when necessary, the recording and reporting of pulse structure details with specification of the aforementioned parameters, following the definitions provided in [Fig. 1a](#) and [Table 1](#),<sup>59,60</sup> are highly recommended. Although the standardization of reporting remains challenging due to significant variation across platforms, the pulse structure should be recorded and reported consistently at a minimum of 1 user-defined reference point. The temporal resolution of the recording at the reference point should be no coarser than the individual pulse duration (ie, on the order of microseconds), with the measured dose rate ([Table 1](#)).<sup>61</sup> Finer-resolution (submicrosecond) subpulse structure reporting is encouraged if achievable. With advancing UHDR-RT dosimetry technologies (see Dosimeter Requirements section), recording at multiple points and dimensions with high spatial and temporal resolutions is desirable. When direct measurement is not possible, meaningful information on the spatiotemporal distributions of pertinent parameters can be obtained based on delivery information from a reference point for well-characterized beams with the use of established calculation models such as analytical or Monte Carlo radiation transport models.<sup>55,62</sup>

## Proton beam therapy

Current UHDR irradiation with proton beams has been proposed and/or performed using several techniques, including (1) scattered transmission, (2) scattered transmission with range modulation, (3) PBS with transmission, and (4) PBS with range modulation.<sup>6,29-32,39,63-65</sup> With further technical development in beam structures and planning techniques, modification of the reported beam parameter

requirements for spatiotemporal dose distribution reconstruction in patients is anticipated.

UHDR irradiation has been performed with clinical isochronous cyclotron, synchrotron, and synchrocyclotron-based proton machines that generate quasicontinuous or pulsed beams.<sup>6,39-41</sup> Under the assumption of a quasicontinuous beam from cyclotron accelerators or within 1 spill from synchrotron accelerators, the following are recommendations for the reporting of UHDR proton therapy beam parameters. For a passive scattered beam without dynamic range modulation, the minimal recommended recordings are of the dose and mean dose rate at a user-defined reference point per beam, providing the possession of prior knowledge of the aforementioned parameters of interest for conventional proton therapy. For scattering with dynamic range modulation and use of a modulation wheel, temporal modulations per range modulation step should be recorded as the dose is delivered by sweeping through the depth. For active scanning beams, the recording of dynamics is further complicated by the scanning pattern and speed and any potential fluctuation in the beam intensity ([Fig. 1b](#)).<sup>63,66,67</sup> Thus, the parameters to report, including the spot position, profile, dose, and dose rate in spatial (millimeter scale) and temporal (microsecond scale) domains, ideally would be acquired from a cross-sectional reference plane at sufficiently high resolution to resolve the quantities of interest. For transmission beams, the reference plane can also be defined at the exit side. Although technologies enabling such measurement are emerging with prototypes being tested,<sup>66</sup> they are not yet ready for routine deployment (see Dosimeter Requirements section). Thus, the recording of the proton spot energy and intensity and spot delivery time structure at a resolution to resolve the dose per spot at a user-defined reference point (as in the example shown in [Fig. 1b](#)) is recommended as a reporting minimum. It is ideal to record the delivery time structures at resolutions much finer than the spot duration (less than a few microseconds). Similarly, the reporting of spatiotemporal distributions of the parameters of interest, calculated for each voxel in the irradiation volume and based on the delivery information recorded via analytical



**Table 1** Reportable parameters for ultrahigh dose rate electron and proton beam deliveries

Parameter	Definition	Electron	Cyclotron	Synchro-cyclotron	Synchrotron
Beam energy		Nominal energy	Delivered energies at nozzle	Delivered energies at nozzle	Delivered energies at nozzle
Pulse repetition rate	Number of pulses per second	<400 Hz	Near 100 MHz	<1000 Hz	<1 Hz for spills
Duty cycle	Ratio of pulse ON time to OFF time	1/2000-1/100	Quasicontinuous	<10%	2 to tens of milliseconds per spill
Temporal pulse structure	Temporal sequence of pulses from the beginning to end of delivery, including the intervals between fields	To resolve individual pulses and pulse-shaped structures	To resolve per spot delivery time structure if PBS	To resolve beam pulses in addition to spot delivery time structure if PBS	To resolve spill duration and intervals, in addition to spot delivery time structure if PBS
Beam intensity	Number of particles irradiated	Per beam, can be replaced by the beam dose	Per beam and per spot if PBS	Per beam, per pulse, and per spot if PBS	Per beam, per spill, and per spot if PBS
Cumulative dose per delivery	$D$ in Fig. 1a at user-defined reference point(s)				
Dose per pulse	$D_p$ in Fig. 1a at user-defined reference point(s)	Per beam pulse	Per spot if PBS	Per beam pulse in addition to per spot if PBS	Per spot if PBS
Instantaneous dose rate	$\dot{D}_p$ in Fig. 1a at user-defined reference point(s)	$10^4$ - $10^6$ Gy/s	$\dot{D}_p$ within a spot duration if PBS	$\dot{D}_p$ within a spot duration if PBS	$\dot{D}_p$ within a spot duration if PBS
Mean dose rate per beam	$\bar{D}$ in Fig. 1a for each beam at user-defined reference point(s)	40-3000 Gy/s	Delivery-specific spot pattern if PBS	Delivery-specific spot pattern if PBS	Delivery-specific spot pattern if PBS
Mean dose rate per fraction	$\bar{D}$ in Fig. 1a for each fraction at user-defined reference point(s)	Delivery-specific fields	Delivery-specific fields	Delivery-specific fields	Delivery-specific fields
Volumetric dose-rate distribution per beam and per fraction	Temporal dose distribution at each voxel in the treatment volume	Derived via beam modeling and monitoring data	Derived via beam modeling and monitoring data	Derived via beam modeling and monitoring data	Derived via beam modeling and monitoring data

*Abbreviation:* PBS = pencil beam scanning.

or Monte Carlo calculations, is encouraged.<sup>29,30,68,69</sup> The results can be used to calculate protocol-defined dose rates in clinical trials.

Special consideration should be given to the beam temporal structure generated by synchrotron- and synchrocyclotron-based systems, for which the assumption of a quasicontinuous beam for single field delivery no longer holds. With synchrotron-based systems, proton spill from the accelerator typically supplies a number of spots, and the interval before the next spill generation is longer (ie, a few seconds). Thus, the instantaneous spot dose rate within a spill and the interval between spills should be recorded. For synchrocyclotron-based systems, the time-resolved dose

delivery at the temporal pulse structure of the extracted beam with a pulse repetition rate of about 1 kHz and duty cycle of a few percent at a reference point should be recorded and reported<sup>40,70</sup> in addition to the parameters for quasicontinuous beams. Compared with those for cyclotron-based PBS beams, the reporting requirements for synchrotron- and synchrocyclotron-based UHDR PBS beams impose additional delivery timing information for the resolution of per-pulse and spill delivery in addition to the capture of the cross-sectional spot scanning delivery.

When multiple fields are involved in electron and proton UHDR delivery fractions, the time intervals between the completion of one field and start of the other field must be

recorded at millisecond-scale resolution. In addition to the aforementioned dosimetric recordings, the working group recommends the recording and reporting of any interruption to beam delivery, actions taken to resume delivery, unexpected discrepancies, deviations, and outliers during delivery. The group also encourages UHDR-RT system manufacturers to take these issues into consideration in the development of their intrinsic delivery monitoring and interlock devices and to make log files accessible to end users. Reportable parameters listed in Table 1 are also recommended to be included in the future Digital Imaging and Communications in Medicine (DICOM) RT delivery report for UHDR deliveries.

## Definition and Control of Safe UHDR Beam Delivery

Safe UHDR-RT delivery is defined as the delivery of radiation to a tissue volume in accordance with the protocol-defined dose, dose rate, and radiation modality and the approved spatial dose distribution from the prescribed treatment plan. Although the safety of modern RT systems has improved dramatically over time, UHDR beam delivery control and safety pose unique challenges pertaining to the instantaneous nature of UHDRs. UHDR beam intensities are several hundreds to thousands of times greater than those of conventional clinical beams.<sup>37</sup> For electron beams, each pulse (with a repetition period of milliseconds and duration of several microseconds) carries sufficient electrons to cause severe ion recombination in conventional transmission air-filled monitor chambers, which are used for beam monitoring in conventional RT (CONV-RT). Such ion recombination effects need to be characterized and compensated for accurate recording of the delivered dose.<sup>71,72</sup> Although correlations of the UHDR-RT dose, dose rate, and dose distribution with biologic effects are under investigation, the potential hazards of various UHDR-RT delivery failures are discussed in this section. Recommendations are made for the tolerance of delivery parameters based on the frequency and severity of potential failures in CONV-RT.

The protocol-defined dose is to be delivered correctly under UHDRs. Delivery machine performance must be stable and consistent with commissioning values. This includes characteristics that drive the physical dose distribution, such as depth dose/beam energy, dose linearity, spot position accuracy, output factors, and others. There is no current evidence to support deviation from current TG-40, TG-142, and TG-224<sup>72-74</sup> guidelines, so at present values in these guidelines remain the most reasonable tolerances. Other characteristics for UHDR-RT are influenced by the dose rate and require some additional consideration.

## Output dependency on the dose rate in the beam monitor chamber

The high instantaneous current in a pulsed beam causes severe ionization recombination in most transmission-type

air-filled monitor chambers. The 2-voltage method and Boag's method<sup>73,74</sup> are inadequate for the correction of ion recombination loss at this level. We recommend that a monitor chamber with a flat (or fully characterized) response to all possible dose rates and pulse structures be used for UHDR-RT to maintain <3% output variation.

## Motion management

The active management of intrafractional motion and residual setup error is critical to minimize delivery error in hypofractionated UHDR-RT. The rapid delivery of UHDR treatments to fields covering human patient tumor targets can increase the likelihood of partial misses in the presence of target motion. Passive and active motion control and/or gated beam delivery from CONV-RT protocols need careful consideration and implementation for accuracy in clinical trials.<sup>75</sup> Motion management techniques should verifiably constrain residual motion to a magnitude much less than that of the target dimensions. The use of respiratory gating techniques is possible with the QA verification of reproducible target positioning, residual motion, and beam triggering within the gating window. These motion management tools should be credentialed before clinical trial participation via an end-to-end moving phantom test.

## Image-guided treatment delivery

The verification of the patient setup and means of immobilization are of critical importance. Conventional kV, cone beam computed tomography (CBCT) and/or 4-dimensional CBCT imaging continue to be important for setup.<sup>56</sup> Real-time image guidance provides clear benefit to ensure the patient is correctly positioned at the time the radiation is delivered; as a minimum, image guidance immediately before radiation delivery would be necessary to ensure that the setup is proper and the target remains inside the desired radiation portal while the beam is on. However, real-time imaging for motion detection requires a sufficiently fine temporal resolution of a duration much shorter than that of beam delivery, which is very challenging with current clinical imaging systems.<sup>76</sup> Continuous surface imaging can serve as an alternative for the monitoring of intrafractional target motion; the correlation between the surface position and the internal anatomy must be verified.<sup>77</sup> Emerging in vivo and functional imaging techniques<sup>57,66,78</sup> are promising for the monitoring of pulse-to-pulse beam delivery. Image guidance credentialing should be mandatory for any FLASH clinical trial.

## Accessories

Clinic processes and workflows using treatment or patient specific matching accessories for UHDR-RT, such as the ridge filter and aperture, can be beneficial. Such devices

require robust positional quality control. Any change in the latching status would need to result in the immediate termination of the beam.

## Shielding

UHDR-RT increases the instantaneous dose rate by several orders of magnitude. To accrue patients to a UHDR-RT trial, it will be necessary that participating institutions have shielding that can meet regulatory requirements for UHDR beams.<sup>79,80</sup>

## Dosimeter Requirements

### Dose measurement

The introduction of UHDR beams raises new dosimetry challenges.<sup>70,81</sup> Dosimeters for UHDR beams need to record the doses and dose rates accurately and reliably. The current clinical reference dosimetry tools for calibration, verification, and QA are air-filled ionization chambers that are traceable to national standard laboratories.<sup>74,82,83</sup> However, ionization chambers are known to exhibit dose rate–dependent ion recombination effects,<sup>84</sup> and great care and scrutiny are required when they are used for reference dosimetry under UHDR beams. An ideal UHDR dosimetry

system must have well-defined dose-response curves and dose-rate independence or a well-characterized dose-rate dependence relationship. It should have little energy dependence or have dose and dose-rate response curves characterized under specific beam energies. In addition, a dosimetry system used to measure the flatness and symmetry of UHDR lateral beam profiles needs to provide sufficient spatial resolution for this purpose. The use of many traditional dosimeters with UHDR beams has been explored (Table 2).<sup>81</sup> The upcoming American Association of Physicists in Medicine (AAPM) report on FLASH dosimetry (TG 359) will provide further review and recommendations for dose measurement.

### Dose-rate measurement

Another important component of UHDR dosimetry is dose-rate measurement. Given the lack of a well-established definition of the dose rate (see FLASH-RT Delivery Reports section), a definition must be set at the initiation of a clinical trial and adhered to throughout the trial duration to facilitate the acquisition of consistent and reproducible observations. The dose-rate dosimetry system must record the differential dose accumulation history and associated timing information. It must be verified and validated against an independent measurement to verify compliance with the dose rate defined in the trial protocol.

**Table 2** Dosimeters and their characteristics for electron and proton UHDR beams

Dosimeters	Dose-rate independent	Radiation damage	2-Dimensional spatial resolution	LET independent	Readout immediately after delivery	Macropulse dose information
Radiochromic film	Y	No reuse	Y	N	N	N*
OSLD	Y	N	Y*	Y	N	N
TLD	Y	N	N	Y	N	N
Alanine	Y	N	N*	Y	N	N
Calorimeter	Y	N	N	Y	Y	Y*
Silicon diode detector	Y*	Y	Y*	Y	Y	Y*
Diamond detector	Y*	N	N*	Y	Y	Y*
Cylindrical ion chambers	N	N	N	N	Y	N*
Thin-gap parallel plate chamber	Y for P	N	Y	N	Y	Y*
Small-volume cylindrical ion chamber	Y for P	N	Y*	N	Y	Y*
Faraday cup	Y	N	N	Y*	Y	Y*
Beam current transformer	Y	N	N	Y	Y	Y*
Plastic scintillator	N	Y	Y	N	Y	Y*
Inorganic scintillator	Y*	N*	Y*	N	Y	Y*

*Abbreviations:* LET = linear energy transfer; N = No; N\* = No, except for highly specialized settings or most likely not; OSLD = optically stimulated luminescent dosimeter; P = proton; TLD = thermoluminescent dosimeter; Y = Yes, demonstrated and in use; Y\* = Yes, but with caveats or to be demonstrated.



The selection of a dose-rate verification technique depends on the radiation type and delivery modality. For instance, a broad UHDR electron field differs from a proton PBS field, temporally and in terms of the spatial structure. In addition, the dose-rate definition may influence the optimization of UHDR treatment plans (see Treatment Plan Reporting section). Thus, UHDR implementation should be verified with time-resolved dose measurements using a sampling rate that is suitable for the time structure of beam delivery. For pulsed beam delivery, if the micropulse time structure is too short to be feasibly captured at a submicrosecond time scale, then the dose reading rates should be sufficiently fast to reproducibly capture the macropulse structure with another system recording only the pulse timing.

Statically collimated electron and passive scattered proton fields can be spatiotemporally constant, which allows the extrapolation of a point measurement of the dose rate to the rest of the field. Various systems have been used to obtain UHDR delivery timing information; examples include a monitoring chamber,<sup>34</sup> a diamond detector,<sup>85,86</sup> radioluminescence and Cherenkov emission,<sup>87,88</sup> and a beam current transformer.<sup>58</sup> If the beam on and off signals are obtained from another system (eg, beam control electronics), then the mean dose rate can also be inferred with a passive dosimeter.

Spatiotemporally varying beams, such as those employed in proton PBS, pose additional challenges for dose-rate measurement. The dose from single PBS spot contributes varying amounts to the entire volume with a time structure characteristic of the PBS pattern (Fig. 1b).<sup>30,63</sup> Thus, at least 2-dimensional (2D) planar time-resolved dose measurement with sufficient spatial resolution is required to detect the dose modulation and gradients over time. Current log files that vendors build into systems can provide time-resolved 2D spot delivery information,<sup>58,63</sup> but the sampling frequency needs to be adapted to a time scale shorter than that of UHDR spot or pulse delivery (ie, a few to tens of microseconds).

To extract the spatial dose and dose rate information, software (independent or integrated with the treatment planning system) should be available for the analysis of the delivered timing and dose information, display of a 2D or 3-dimensional (3D) dose-rate map, and calculation of protocol-specific dose-rate metrics analytically or via Monte Carlo simulation. The 1-dimensional point measurement can then be extrapolated with a known 2D dose profile, such as percentage depth dose data, from the treatment planning system (TPS) or commissioning data.<sup>46,55</sup>

In summary, FLASH-RT clinical trials impose new and challenging requirements on dosimeters, which must record the integral dose, time-resolved point dose, or 2D dose delivery accurately, reproducibly, and at sufficient sampling frequency under UHDR beams (Table 2). Various efforts are ongoing, and further development is needed to test and validate suitable systems for UHDR beam reference dosimetry, characterization, and monitoring in FLASH-RT clinical trials.

## FLASH-RT System Credentialing and QA

### Imaging and Radiation Oncology Core credentialing

Particularly in multi-institutional clinical trials, it is important to ensure that all institutions can and do deliver the intended treatment accurately and consistently.<sup>89</sup> To be eligible for participation in the National Clinical Trials Network (NCTN), institutions are required to undergo (1) site qualification (eg, annual output checks, which all institutions perform and are a prerequisite for participation in any trial), and (2) credentialing (eg, intensity modulated RT phantom irradiation under defined conditions), which is performed by potential participating institutions in response to the requirements of specific protocols. The Imaging and Radiation Oncology Core (IROC) manages both of these steps for NCTN trials.<sup>90</sup> We anticipate that the same structure will be required for NCTN FLASH/UHDR RT clinical trials.<sup>56</sup>

Site qualification should involve a high-level review of the institution's capabilities and clinical practices. As it would be specific to the UHDR machine for a FLASH-RT trial, prior institutional qualification based on a standard LINAC or proton accelerator would not be sufficient. For FLASH-RT clinical trials, site qualification should include the following:

1. Ensuring that the UHDR machine is Food and Drug Administration approved or covered by an investigational device exemption
2. Ensuring that the UHDR machine is capable of delivering the dose distribution and dose rate required by the protocol
3. Ensuring that the appropriate dosimetry and ancillary equipment (eg, Accredited Dosimetry Calibration Laboratory (ADCL) calibrated detectors, image guidance, motion management systems) is available for accurate UHDR delivery
4. Ensuring that the programmatic practices (eg, disease sites treated, planning techniques, typical margins, application of recording and verification systems) meet the guidelines established by the National Cancer Institute and IROC
5. Confirming basic dosimetry and beam timing characteristics

Items 1 to 4 could be assessed using questionnaires and would rely on expert consensus developed through preclinical trials and with NCTN principle investigators (PIs). Broad information on FLASH-RT intent (ie, treatment prescriptions) and delivery systems, for example, would facilitate IROC's evaluation of the treatment planning, delivery, and verification processes at a given institution, and might provide insight into how community standards compare to clinical trial objectives. The information that should be collected includes (1) the general characteristics of the UHDR

beam delivery system (eg, beam pulsing structures and dose rate definition); (2) measurement results related to absolute dosimetry at different dose rates, including conventional clinical dose rates; and (3) descriptions of procedures for FLASH-RT prescription, pretreatment QA, and handling of treatment interruptions.

The independent confirmation of basic dosimetry and beam timing characteristics is more involved, requiring remote or on-site auditing, and represents a major current gap in knowledge and capabilities. This task is performed annually for all machines at conventional dose rates; less-frequent monitoring for UHDR modalities is difficult to imagine, but annual on-site auditing would quickly become impractical. The independent auditing of delivered doses is well established and could likely be extended directly to UHDRs. The most challenging, and likely most important, component of dosimetry auditing would be the verification that the protocol specific dose rate is achieved. This issue is complicated by the lack of a standard UHDR definition. At minimum, ensuring that one well-defined UHDR is achieved would be essential. However, such testing may be very challenging to implement remotely. On-site auditing is technically more straightforward but may be cost prohibitive. Ideally, and particularly as questions about the dose rate required remain unanswered, quantitative documentation of the pulse structure, dose per pulse, and other dose-rate metrics is critical. Credentialing requirements will be developed and included in each specific protocol.

Protocol-specific credentialing involves deeper investigation of the institution's capabilities and treatment process through the end-to-end testing of the treatment simulation, planning, and delivery. This process verifies that the intended physical dose and dose rate are delivered to the intended location, and it should be performed under clinically realistic conditions. At present, FLASH-RT trials are conducted with relatively simple clinical conditions and single unmodulated fields. This setting should guide current credentialing requirements (regardless of the treatment modality). For treatment planning algorithms that have been previously credentialed in non-UHDR settings, there may not be a need to retest complex heterogeneities or structures when the dose rate is the only part of the delivery changing (although the optimization of the dose and dose rate is desirable). Credentialing requirements for a given protocol may extend beyond end-to-end testing (eg, image guided RT credentialing); such testing should be considered a minimum requirement.

One gap in the IROC's current credentialing practice is related to the review of electron treatments. Although the electron output is checked regularly for reference conditions, no electron phantom is currently used for protocol-specific credentialing. Additionally, electron treatment planning algorithms have not been reviewed; in contrast, the use of only certain proton and photon algorithms is allowed in clinical trials. Thus, electron UHDR treatments may require more comprehensive credentialing than do photon or proton UHDR protocols.

As for non-UHDR clinical trials, all UHDR-RT site qualification and credentialing should be independent and consistent. The IROC should provide the entire measurement system (including the phantom and dosimeters) to facilitate the measurement of the dose and dose rate for a given beam delivery modality.

Other scientific and logistical questions also exist. Should credentialing be conducted more than once to verify the delivery system's ongoing or long-term stability? If multiple machines or types of machine are used at a single institution, should unique credentialing of every machine be required or is complete credentialing of a single machine sufficient? What tolerance should be used in credentialing testing, particularly for dose-rate evaluation? These issues require not only scientific evaluation but also practical consideration given the nature of clinical trials.

Finally, credentialing should evolve to include more complex anatomic conditions as FLASH-RT trials evolve, for example to include moving targets, conformal or multifield treatments.

## IROC case review

Patient-specific case review for clinical trial enrollment is another major component needed to ensure trial consistency and quality. In addition to the procedures required for the evaluation of planned RT using conventional dose rates, UHDR treatment plan evaluation needs to be voxel based, including examination of the dose delivery time structure and the parameters associated directly with this treatment (eg, the beam intensity, beam delivery sequence, and, when used, proton PBS pattern and speed). The protocol and site evaluation should include appropriate UHDR definitions. Close coordination with clinical practice is essential.

## Machine QA

The AAPM task group reports<sup>91,92</sup> suggest various tests and test frequencies for the safety, dosimetric, and spatial components of clinical RT systems. Imaging system QA for image-guided treatment delivery was also established clinically and should be followed.<sup>91-94</sup> However, these established guidelines do not account for the unique consideration of UHDR therapy units. Moeckli et al<sup>53</sup> reported the establishment of the IntraOp electron beam QA program, which entails output and energy constancy checks, based on the AAPM TG-72 recommendations.<sup>95</sup> A UHDR QA program in a clinical trial setting ensures that clinical trials are conducted accurately, while generating data that is reliable and sufficient to answer the questions that are the focus of the clinical trial. A UHDR QA program incorporates the elements of a conventional delivery QA program, while adding specific considerations for the ultra-high dose rates. Important to note, electron and proton UHDR-RT systems are fundamentally different, potentially requiring different approaches, methods, and tolerances in a

modality-specific UHDR QA program. Given the infancy of the UHDR clinical trial environment, it is beyond the scope of this publication to recommend specific quality control (QC) and QA tests and tolerances. Clear and effective QA recommendations are a subject of research in the UHDR community to incorporate data-driven failure modes and effects analysis (FMEA) principles, such as those recommended in AAPM TG-100. That said, because dose, temporal, and spatial characteristics are the most critical parameters to any UHDR clinical trial, tolerances for those parameters should be developed as part of a UHDR QA program that validates, tests, and reports the constancy of machine delivery parameters with appropriate dosimetry systems (see Dosimeter Requirements section).

In addition, treatment delivery records must be maintained for future study and evaluation, as the definition of the dose and dose rate for FLASH-RT effects is still evolving, especially for proton PBS delivery. Treatment records shall conform with the recommendations provided in the FLASH-RT Delivery Reports section and can be obtained or derived from the dosimetry system measurements discussed in the Dosimeter Requirements section.

## Patient QA

Patient-related, UHDR delivery pretreatment QC performed according to current clinical standards<sup>96,97</sup> for intensity modulated x-ray, electron, and proton therapy is needed, while additional QC measurements that include delivery timing information are being developed. This ensures that not only the dose and its spatial characteristics but also the protocol-defined dose rate meet the clinical trial requirements. Just as for machine QA, the UHDR modalities and beam delivery methods are heterogeneous, requiring each specific UHDR therapy machine to have a modality-specific, patient-specific QA program. Point and planar dose-rate QC, particularly compared with the treatment planning system, are important for satisfying the clinical trial design and ensuring reliable data. The clinical trial protocol should include clear patient-specific QA program. Appropriate, and currently limited, detector systems capable of resolving dose and dose rate should be used to ensure trial data quality and patient safety.

## Treatment plan QA

General plan and chart review guidelines for initial, weekly, and end-of-treatment checks have been provided by Task Group 275.<sup>98</sup> Aspects evaluated include the data transfer integrity, accuracy of calculations, image guidance requests, and plan quality. FLASH-RT should follow these recommendations while also including UHDR treatment plan-specific parameters, such as the protocol-specific dose rate, dose per pulse, and pulse width. Any second and independent calculation check should also include these parameters. UHDR planning systems incorporating dose and dose-

rate distribution overlaying a patient image should be displayed and evaluated. A dose and dose-rate-volume histogram should also be displayed and evaluated. Furthermore, the tissue-specific relative biologic effect of a given UHDR modality may be incorporated into the planning system. This effect should be noted in the clinical trial protocol.

## Plan and chart review

The physicist should check the plan to ensure that the dose and dose-rate distributions reflect the protocol specifications. The physicist should also perform standard plan and chart reviews to ensure that the requested imaging guidance and motion management would ensure safe UHDR delivery. The analysis of UHDR treatment plans' robustness will need to be expanded from standard robustness analysis to include the reliability of defined dose rate achievement.

The physicist should also review the plan with the physician to ensure that if the UHDR is not achieved during RT, the plan will still be safe for target irradiation with adequate sparing of normal tissue as with conventional dose rates.

## Special QA considerations

The end effect, partial treatment functionality, and log file QA are relevant topics for CONV-RT, but essential for UHDR treatments.

### End effect dose

In 10CFR35, the Nuclear Regulatory Commission (NRC) defines a medical event by, among other indications, misadministration exceeding 20% of the total prescribed dose or 50% of the prescribed fractional dose.<sup>99</sup> These tolerances are often extended to nonisotopic treatments by various state regulatory agencies. Furthermore, International Electrotechnical Commission (IEC) 60601-2-64 sets the standard that no accelerator shall deliver >10% of the dose after an interlock is triggered.<sup>100</sup> The end effect or shutter dose is quantifiable, defined as the residual dose delivered from the time of interlock detection to that of dose termination.<sup>101,102</sup> Modern CONV-RT machines readily meet these requirements. However, for UHDR-capable machines used for FLASH-RT, the primary beam monitor and its interlock triggering software and hardware will need to have much faster responses than do CONV-RT setups and will need to be established for UHDR delivery to correctly record delivery dose and timing information. Due to the extremely short (millisecond-order) beam-on times, it is impractical, if not impossible, to test the door interlocks or manual emergency beam interruption under FLASH-RT delivery conditions. These tests may be performed with irradiation in CONV-RT mode if available.<sup>53</sup>

### Partial treatment

Partial treatment is defined as the partial irradiation of a prescribed treatment field due to treatment interruption (eg,

interlock triggering). For UHDR delivery, partial treatment recovery breaks the prescribed field to be delivered into 2 or more distinct and interrupted fields. The UHDR machine must be able to reconstitute the prescribed field dose from the partial fields, verified with beam monitoring dosimeters. However, partial delivery likely means that the protocol-specific dose rate will not be achieved and can affect the biologic effect of FLASH-RT in the patient. The interval between partial treatment occurrence and treatment resumption should be recorded. Extra care must be taken to ensure that any FLASH-RT clinical trial has a safety mitigation plan in place for partial treatment and irradiation. For example, the FAST-01 trial (ClinicalTrials.gov identifier: NCT04592887)<sup>24,25</sup> was designed so that the physical dose of the prescribed field would be reconstructed in the event of an interlock, partial irradiation, or dose-rate reduction and then delivery to the rest of the field would be performed with CONV-RT, which is an acceptable standard of care.

### Log file QA

QA using vendor-provided log files generated by treatment machine is an acceptable means of machine QA. With development and improvement, the beam monitors of UHDR machines may be the most comprehensive dosimeter systems capable of obtaining measurements such as time-resolved beam intensities and beam positions. Whereas the UHDR treatment commissioning process validates that the log files provide the timing resolution, beam intensity, and position monitoring with independent measurements suitable for specific UHDR modalities, the machine QA and daily QA procedures needs to involve the analysis of those log files before treatment. Furthermore, retrospective analysis of the log files, used solely or jointly with other QA metrology, can be performed to determine the beam dose-temporal distribution for recording and reporting purposes defined in the FLASH-RT Delivery Reports section that is a critical component to ensure safe FLASH-RT delivery in clinical trials.

### Treatment Plan Reporting

Modern CONV-RT treatment planning can generate 3D dose distributions in voxel-based patient images. In typical RT clinical trials, the reporting and sharing of the structures and 3D dose files are needed, usually in standard DICOM format.<sup>103,104</sup> These steps facilitate more detailed and flexible dose analysis for tumors and organs than can be performed with traditional reports on dose-volume-histogram indexes. The analysis and re-examination of the 3D dose distribution potentially allow for improved correlation of clinical outcomes with delivered doses, and the outcome findings and dose distribution can be overlaid on patient images. Thus, the provision and reporting of patient images, target and normal organ contours, and 3D dose distributions is required for FLASH-RT clinical trials.

For UHDR treatment planning, the protocol-specific dose rate should be defined and is expected to be calculated and reported at the voxel level along with timing information for the expected differential dose delivery. Reporting of the 3D dose rate distribution will enable systematic analysis of the combined effect of the dose and dose rate for examination of the FLASH-RT sparing effect in patients in short- and long-term studies. The 3D dose rate and associated beam delivery information in the treatment plan are recommended to be included in DICOM plan information in standardized format. Plan reporting and evaluation should include voxel-based dose delivery time structure and parameters associated directly with UHDR delivery (eg, the beam current, spot delivery sequence, scanning speed, and accessory for beam modification), which are required to generate the dose rate defined in the treatment plan. The time structure of beam delivery is essential for the evolving definition of the FLASH-RT dose rate.

Although the reporting on the optimization algorithm and process is not required, it is expected that the dose and dose rate distributions are optimized in the treatment plan.<sup>69</sup> Various proton FLASH treatment strategies have been investigated with consideration of the beam properties with various dose rate definitions, including beam-specific device designs.<sup>29-32</sup> In addition, it is expected that certain modeling of FLASH-RT biologic effects will be considered in the dose and dose rate planning and optimization.<sup>105</sup>

### Personnel Recommendations

The very short duration of UHDR-RT treatment delivery necessitates higher staffing levels than in current clinical practice. UHDR-RT cases should require the presence of the physicist and physician for each treatment delivery, analogous to stereotactic body RT treatments. The physicist should verify all treatment plan parameters prior to each beam delivery as well as the pretreatment imaging and alignment in an online fashion. In addition, physicists should be responsible for performing or verifying that the appropriate machine QA and patient-specific QA are performed before each UHDR-RT treatment. Adequate image guidance should be employed to ensure the localization to the target and proximity of nearby organs at risk before each UHDR-RT fraction. It is critical that for each of the treatments, the attending physician reviews and approves the target localization, proximity of nearby organs at risk, prescription, dose, and dose rate before beam delivery.

### Investigator Training Recommendations

While several institutions are conducting extensive research in FLASH, there will likely be a large number of FLASH-capable machines available in the near-future. This means that many clinics will treat FLASH patients—including clinical trial patients—without prior FLASH training or clinical experience. As multi-institutional clinical trials for FLASH



**Table 3 Summary of challenges and technical gaps for FLASH radiation therapy clinical trials and future outlooks**

Topics in FLASH clinical trials	Challenges and technical gaps	Future outlook
Reporting parameters	<ul style="list-style-type: none"> <li>• Reporting the delivery time structure is not needed in current clinical practice.</li> <li>• UHDR-RT systems have drastically different beam structures.</li> <li>• Multiple definitions of dose rates exist.</li> <li>• No clear understanding on if FLASH dose threshold exists and which definition of dose rate is related to the observation of FLASH effects.</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor the spatiotemporal beam delivery at a timing resolution that resolves every pulse and at finer resolution if possible.</li> <li>• Build a recording and reporting system to derive and report the 3-dimensional voxel-based dose and dose rate distributions with monitored beam intensity, position and time structure.</li> </ul>
Dosimetry	<ul style="list-style-type: none"> <li>• Traditional ion chamber for reference dosimetry suffers from ion recombination effects under UHDR irradiation.</li> <li>• Various dosimeters are being tested for their accuracy and reliability in dose measurements under UHDR.</li> <li>• Systems that record UHDR delivery time structure are also under development.</li> </ul>	<ul style="list-style-type: none"> <li>• Evolving dosimetry technologies are to be developed to reliably measure the integral dose, differential dose with associated time structure.</li> <li>• Uncertainties in the UHDR dose and dose rate measurements for various modalities are to be assessed.</li> <li>• Establish dosimeter reference standard for UHDR beams.</li> </ul>
Safety	<ul style="list-style-type: none"> <li>• Beam control system needs to have much quicker response to beam interruption and termination.</li> <li>• Stability and repeatability in the deliveries of desired dose and dose rate need to be checked.</li> <li>• Safety on patient partial delivery.</li> <li>• Facility shielding needs to be assessed for UHDR-RT treatments.</li> </ul>	<ul style="list-style-type: none"> <li>• UHDR system development groups and vendors work on solutions for faster beam controls, partial delivery monitor, and treatment resume process.</li> <li>• Employ appropriate dosimetry system to check the UHDR beam qualities.</li> <li>• Shielding assessment under the work load of FLASH clinical trials.</li> </ul>
IROC quality assurance	<ul style="list-style-type: none"> <li>• There are no established standards for UHDR-related parameters.</li> <li>• Appropriate dosimetry for UHDR dose and dose rate measurements is under development.</li> <li>• Appropriate phantoms for credentialing are needed.</li> <li>• Patient-specific case review for clinical trial enrollment.</li> </ul>	<ul style="list-style-type: none"> <li>• Develop IROC/NIST traceable standards for dose and dose rate and validate in UHDR radiation systems.</li> <li>• Appropriate phantoms are to be developed and used for end-to-end UHDR treatment credentialing.</li> <li>• All site qualification and credentialing should be independent and consistently performed.</li> <li>• Patient-specific case review should include beam time structure for voxel-level dose rate analysis and verification.</li> </ul>
Treatment plan	<ul style="list-style-type: none"> <li>• Current TPS does not generate user-defined, voxel-based dose rate in patient treatment volume by incorporating the beam delivery time structure.</li> <li>• Similar to dose-volume histogram, dose-rate-volume histogram needs to be developed and displayed.</li> <li>• Optimization on both dose and protocol-defined dose rate.</li> <li>• FLASH biologic driven planning is likely to be necessary.</li> </ul>	<ul style="list-style-type: none"> <li>• TPS vendors work with FLASH clinical community on UHDR treatment planning including calculation, optimization, and reporting of the dose and dose rate.</li> <li>• FLASH biologic driven TPS using established relationship of FLASH sparing effects with treatment dose and dose rates.</li> </ul>
Clinical QA	<ul style="list-style-type: none"> <li>• Machine QA on UHDR-related parameters were not established.</li> <li>• Patient-specific QA on UHDR-related parameters such as dose and dose rate in point, 2-dimensional, and 3-dimensional needs to be established with appropriate dosimetry system.</li> <li>• QA on the workflows under special situations such as partial treatment needs to be established.</li> </ul>	<ul style="list-style-type: none"> <li>• Stabilities of the beam parameters dictate the frequency of the QA on these parameters.</li> <li>• Develop complete machine and patient QA programs including UHDR-related parameters.</li> <li>• Vendor-provided log files can be an important component in establishing the QA programs.</li> </ul>

(Continued)



**Table 3** (Continued)

Topics in FLASH clinical trials	Challenges and technical gaps	Future outlook
IGRT and motion management	<ul style="list-style-type: none"> <li>• Patient setup and image guidance for UHDR delivery is challenging.</li> <li>• Motion management for UHDR delivery needs development.</li> </ul>	<ul style="list-style-type: none"> <li>• Develop motion control and mitigation strategies in treatment planning and delivery.</li> <li>• Develop ultrafast and pulse-based in vivo dosimetry.</li> <li>• Develop advanced functional and biologic image guidance.</li> </ul>
<p><i>Abbreviations:</i> IGRT = image guided radiation therapy; IROC = Imaging and Radiation Oncology Core; NIST = National Institute of Standards and Technology; TPS = treatment planning system; UHDR-RT = ultrahigh-dose-rate radiation therapy; QA = quality assurance.</p>		

begin to accrue patients, it will be imperative that participating institutions have training specific to the complexities of the trial. For example, NCTN protocols for proton therapy often include more frequent PI meetings to discuss lessons learned and protocol deviations observed during the initial accrual to the trial. These collaborative training sessions help reduce deviation rates on the protocol and are highly recommended for FLASH clinical trials.

## Summary and Discussion

Preclinical research conducted with small animal models has shown that FLASH-RT has the potential to improve the therapeutic ratio between the tumor response and normal tissue toxicity. As interest in the incorporation of FLASH RT into clinical practice builds, we anticipate that many FLASH-RT clinical trials will open in the future. In this summary from the NCFWG on considerations for such trials, we review the current status of UHDR deliveries, identify technological gaps, and recommend standards. The challenges and technical gaps that must be considered for FLASH-RT clinical trials and future outlooks are summarized in Table 3. The discussions in this article focused on electron and proton UHDR modalities. With the development of UHDR delivery with other modalities, such as heavy-ion and photon beams,<sup>16,44,51,106</sup> future work in the credentialing of FLASH-RT clinical trials based on these modalities is anticipated.

Every new modality comes with benefits and challenges. FLASH treatment is delivered in a fraction of a second, much shorter than in current clinical practice. The understanding of the radiobiology, fractionation, treatment modalities, dosimetry, and QA for UHDRs is evolving. As described in the FLASH-RT Delivery Reports section, the use of multiple UHDR modalities and systems for FLASH-RT have been explored. FLASH clinical trials conducted by the NRG Oncology Cooperative Group and other trial groups will require IROC credentialing of UHDR systems and likely an investigational device exemption from the Food and Drug Administration for these delivery systems. Although the current standard/basic clinical trial-specific requirements for conventional treatment reported in various NRG and other groups' clinical trial protocols and publications<sup>56</sup> still hold, FLASH-RT clinical trial-specific

requirements need to be developed and validated. The committee has recommended QA, monitoring, and reporting of critical UHDR treatment parameters, such as the beam intensity and delivery time structure, dose per pulse or PBS spot, and integral dose in 3D voxel-based treatment volume. These requirements, in turn, add new challenges to current dosimetry systems and open up opportunities for the development of dosimetry technology for the measurement and recording of differential UHDR dose with time stamp. Measurement uncertainties in UHDR dosimetry systems need to be understood. Concerns about patient safety should be addressed during clinical trial design, with a protocol and validated mitigation strategy defined for the case of any potential discrepancy or deviation from the prescribed dose and dose rate. Image guidance and motion management for UHDR treatment need to be developed. Machine and patient-related QA programs are needed to address UHDR treatment-specific aspects with appropriate dosimetry systems. Further development of treatment planning systems and plan reports is needed for dose and dose rate optimization and calculation with the incorporation of machine- and beam-specific delivery parameters.

Currently, many questions about the effects of FLASH-RT remain. The existence of an UHDR dose threshold, the dose rate threshold for the observation of FLASH-RT effects, and acceptable and optimal treatment fractionation schemes remain unclear. Multiple definitions of the dose rate exist, both for electron and proton PBS UHDR deliveries. Many preclinical studies investigating FLASH radiobiology mechanisms are ongoing. FLASH-RT effects may be tissue specific under certain UHDR delivery parameters. These questions may be answered in part by designing clinical trials by incorporating specific UHDR parameters prospectively in the prescription. The optimal design of such trials is an important question outside the scope of this report. The task of credentialing and QA, which is the focus of this report, is to ensure treatments are reproducibly delivered according to the UHDR prescription across institutions. Correlations of the outcomes of FLASH-RT clinical trials can be performed by retrospectively analyzing reported parameters as specified in the protocol and measured during credentialing, QA, and delivery. The medical physics community needs to work together with physicians, radiobiologists, UHDR treatment system providers,

and treatment planning system vendors to bridge the aforementioned technical gaps and to perform FLASH-RT clinical trials so that patients can benefit from the improved therapeutic ratio that FLASH-RT provides.

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