



Guidelines

GEC-ESTRO ACROP recommendations on calibration and traceability of LE-LDR photon-emitting brachytherapy sources at the hospital level



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ABSTRACT

Prostate brachytherapy treatment using permanent implantation of low-energy (LE) low-dose rate (LDR) sources is successfully and widely applied in Europe. In addition, seeds are used in other tumour sites, such as ophthalmic tumours, implanted temporarily. The calibration issues for LE-LDR photon emitting sources are specific and different from other sources used in brachytherapy. In this report, the BRAPHYQS (BRACHytherapy PHYSICS Quality assurance System) working group of GEC-ESTRO, has developed the present recommendations to assure harmonized and high-quality seed calibration in European clinics. There are practical aspects for which a clarification/procedure is needed, including aspects not specifically accounted for in currently existing AAPM and ESTRO societal recommendations. The aim of this report has been to provide a European wide standard in LE-LDR source calibration at end-user level, in order to keep brachytherapy treatments with high safety and quality levels. The recommendations herein reflect the guidance to the ESTRO brachytherapy users and describe the procedures in a clinic or hospital to ensure the correct calibration of LE-LDR seeds.

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Prostate brachytherapy (BT) treatment using permanent implantation of low-energy (LE) low-dose rate (LDR) sources with photon energies <50 keV, so-called seeds, is successfully and widely applied [50]. In Europe (EU), the current treatment techniques are diverse, using different seed models and equipment. Some clinics use stranded seeds, some others single seeds, and different radionuclides (¹²⁵I or ¹⁰³Pd, but not ¹³¹Cs) are available. Most clinics utilize manual delivery techniques, whereas some others prefer an automatic train assembly and delivery system [48].

In addition to the prostate treatments, seeds are used in other tumour sites. For ophthalmic tumours, eye plaques are used, commonly of the “COMS” type [10], and implanted temporarily in contact with the eye ball. The strength of ophthalmic seeds is typically 5–10 times higher than those used in prostate permanent implants.

Furthermore, seeds can be implanted in the brain to treat metastases [49], in early stage breast carcinoma [44], and in head

and neck cases, although the latter is rare [29]. All these procedures must be performed with very high quality requirements including the use of the correct source strength in treatment planning absorbed dose calculations. If this is not guaranteed, the administered absorbed dose will be inaccurate and it can result in potentially severe patient harm.

The dosimetric issues for LE-LDR photon emitting sources are specific and different from other sources used in BT. The implantation must be timely with respect to the seed strengths to assure the desired absorbed dose is delivered. The end-user in the clinic receives a source strength certificate issued by the vendor containing the average strength of the seed batch and it is up to the user to check it. Mistakes in seed delivery, changes or errors in seed production or changes in calibration procedures on the manufacturer's side cannot be excluded. Practical problems for the end-user to conduct seed strength verifications arise from the fact that sources are delivered sterile and sterility must be maintained during the implantation procedure. This hinders assay measurements unless dedicated assay seeds are delivered as well. Moreover, the seed implant technique is not unique and sources are delivered in different forms of cartridges or packages specific to each implant

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technique. For these reasons, the BRAPHYQS (BRACHYtherapy PHYsics Quality assurance System), working group of GEC-ESTRO ACROP, developed these recommendations to assure harmonized and high-quality seed calibration in European clinics.

Depending on each specific application, there are single or grouped seeds, the number of seeds varies in each implant as well as the source strength (e.g., prostate and ophthalmic sources). In many European hospitals, assay of grouped seeds is performed using specific inserts for well-type ionization chambers. These inserts are different from the ones used during calibration of the well chamber done by the calibration laboratories. Thus, correction (correspondence) factors linking the measurement with the insert for grouped seeds and the source strengths are needed and should be obtained by users. There is a necessity to establish cautions, uncertainties and practical aspects for this methodology. In addition, specific issues of the only existing seed afterloader [48] on the market are faced with respect to seed calibration.

As described later in this report, there are societal recommendations for seed calibration traceability and assaying at the hospital level. These are [5,6,4] from AAPM, and Venselaar et al. ESTRO Booklet n° 8 2004 from ESTRO [60]. The ESTRO booklet adopted the AAPM TG-56 recommendations from 1997 [39]. There are practical aspects for which a clarification/procedure is needed, including aspects not specifically accounted for in these societal recommendations. These necessities together with the adaptation to Europe are the main aims of the present report.

The aim of this BRAPHYQS working package (WP-18) report is to provide recommendations on:

1. Evaluation of source strength at the hospital level from a practical perspective.
2. Level of agreement between the measured source strength by the user and the vendor stated seed/batch value, actions to undertake when the difference exceeds a certain level, including the interaction with manufacturers when a potential discrepancy exists.
3. Recalibration of ionization chambers to maintain the long-term stability of their calibration factors.
4. Knowledge on multi-seed inserts and their relationship to a single (calibration) seed setup.
5. Specific recommendations for seed afterloader (seedSelectron) regarding seed calibration and in general for loose seeds in sterilized cartridges.

The present report establishes all these recommendations along with the relevant discussions in each section: review of current societal recommendations, seed manufacturers' procedures, and traceability of calibrations from standards laboratories to clinical users. The aim of this report has been to provide a European wide standard in LE-LDR source calibration at end-user level, in order to provide high safety and quality levels for BT.

The report reviews the quantities used to characterize the source strength; compiles societal recommendations; describes the seed manufacturing process; covers traceability in calibration; describe current methods to assay grouped and loose seeds; analyses uncertainty related topics to seed measurements and study action levels depending on discrepancies between the seed certificate and user measurements; and finally, summarizes the GEC-ESTRO ACROP recommendations.

Typical clinical uncertainties for calibration of LDR sources for prostate implants can be found in Kirisits et al. [31]. Herein the standard uncertainty for traceable source strength calibrations is combined with appropriate binning data. The resulting 2.7% ($k = 1$) uncertainty were added to an estimated treatment planning uncertainty of 4% ($k = 1$), which results in a combined uncertainty

($k = 1$) of 5%. Uncertainties analysed in the current report are discussed in this context.

The recommendations herein reflect the guidance to the ESTRO BT users and describe the procedures in a clinic or hospital to ensure the correct calibration of LE-LDR seeds. The responsibility to evaluate the calibration remains with the hospital physicist. Moreover, specific national regulations and recommendations must also be considered by the end-user.

The authors want to emphasize that certain materials and commercial products are identified in this report in order to facilitate discussion and methodology description. Such identification does not imply recommendation nor endorsement by ESTRO or the authors, nor does it imply that the materials or products identified are necessarily the best available for these purposes.

Physical quantities to characterize BT source strength

The definition of BT source strength utilizes the measurand air kerma [23]. While "reference air kerma rate" (RAKR) [23] is used in Europe, the "air kerma strength" (S_K) [1] is used in North America. Both relate to the air-kerma rate due to photons of energy greater than δ , at a point located in vacuum on the transverse plane of a sealed, cylindrical BT source. However, while RAKR is specified at a reference distance, $d_{ref} = 1$ m from the source centre, the S_K is defined through a multiplication with the square of the distance to the source centre.

The unit of RAKR is $Gy h^{-1}$ and that of S_K is $Gy m^2 h^{-1}$. Note that since $d_{ref} = 1$ m for RAKR, the two quantities are numerically equal (although not dimensionally). The unit of air kerma strength, noted U, is often seen in the context of source strength of low energy seeds: $1 U = 1 \mu Gy m^2 h^{-1} = 1 cGy cm^2 h^{-1}$. As these are European recommendations, we will in the following use RAKR units, unless otherwise specified.

For traditional reasons, vendor certificates for source strength often provide the antiquated quantity apparent activity (A_{app}) in units of mCi. Apparent activity is not a traceable quantity, does not serve the TG-43 formalism, and must be avoided.

Using the TG-43 formalism for dose calculation in treatment planning [38,48,23], but with reference to RAKR and not to S_K , the absorbed dose rate to water, $\dot{D}(r, \theta)$, delivered to a patient is directly proportional to the \dot{K}_δ (or S_K) of the actual source:

$$\dot{D}(r, \theta) = \dot{K}_\delta \cdot \Lambda_{r_0} \cdot \frac{G_X(r, \theta)}{G_X(r_0, \theta_0)} \cdot g_X(r) \cdot F(r, \theta) \quad (1)$$

In Eq.(1), \dot{K}_δ is the RAKR and Λ_{r_0} is a dimensionless constant, called the dose-rate constant, defined as absorbed-dose rate at a specified reference point per unit RAKR. The value of Λ_{r_0} is considered characteristic of a source design. The product of $\dot{K}_\delta \Lambda_{r_0}$ then gives the absorbed-dose rate at the reference point (r_0, θ_0). For photon seed sources in conventional BT, the reference point is often specified at 10 mm from the source in a perpendicular bisecting plane, i.e., ($r_0 = 10$ mm, $\theta_0 = \pi/2$). All factors of Eq. (1) except \dot{K}_δ are predetermined (calculations, measurements, Monte Carlo simulations).

Current societal recommendations

There have been incidences where BT sources have been characterized improperly by the manufacturer or ordered incorrectly by the medical physicist [42,17,18,21]. Further, there have been incidences where confusion about the units of BT source strength has resulted in patient treatment errors [42]. While historical units of mg-Ra-eq and mCi may still be in use, ESTRO and numerous other bodies have averred that RAKR is the necessary metric [60].

This is due to its use for transferring calibration traceability from a calibration laboratory to the instrumentation used by the clinical medical physicist for measuring source strengths. The historical units of mg-Ra-eq and mCi simply are not traceable quantities for photon-emitting BT sources, and their clinical use has resulted in patient treatment errors equal to the differences in their conversion factors, i.e., 1.270 U/mCi for ^{125}I and 1.293 U/mCi for ^{103}Pd [38]. Consequently, it is imperative that source strength (in terms of RAKR or S_K) be used in *all* aspects of patient care, while mCi (related to contained activity) should be used only for transportation labelling purposes and licensing limits.

Accepting the results of third-party calibration services to assay BT source strength would help to reduce the workload of physicists involved in BT. However, issues are raised in relationship to patient safety, legality, and medical physicist role [4]. In conclusion, it is imperative that the source strength reported by the manufacturer be independently checked by the recipient, i.e., mostly the onsite clinical medical physicist. Since 1994, the AAPM TG-40 Report [32] stipulated for its clinical medical physicist members, largely in the U.S., the requirement for independent assaying of BT sources. Reinforcement for performance of this task was made in the AAPM TG-56 Report [39], which was then cited in other reports or societal guidelines [63,37,60] such as by the ABS, ACMP, ACRO, and ESTRO.

More recently, in the AAPM Report 98 [4], recommendations were made on the necessary sample size and acceptable tolerance for comparing a source-strength assay with the manufacturer-reported value. The recommended sample size accounts for the number of BT seeds and their configuration (such as sterility and their accessibility in strands or cartridges) being the fewer of 5% or 5 seeds from a separate order, or the larger of 10% or 10 seeds from an order of loose nonsterile seeds. The recommended tolerances and resulting actions were similarly specific to the circumstances at hand, but were typically >5% for consulting with the manufacturer to resolve differences.

The AAPM Report 98 was interpreted in the AAPM TG-167 Report for innovative BT devices and applications [40], and by the American College of Radiology (ACR) and AAPM for clinical practice standards for the performance of LDR BT.

These recommendations were endorsed by the Australasian College of Physical Scientists and Engineers in Medicine [13] and the Canadian Partnership for Quality Radiotherapy [11].

With respect to the European countries, NCS (for the Netherlands and Belgium) [41] adopted the AAPM Report 98 recommendation [4] on the number of seeds to be measured (10% of the seeds with a minimum of 10 seeds) and the action levels. However, tolerance levels on the measured source strength for an individual seed were not set. While NCS recommendations are not legally binding, not following them could be considered as a professional error during a lawsuit.

According to the German guidelines “Strahlenschutz in der Medizin RS II 4 – 11432/1” from 2011 [16], the manufacturer or vendor allocates the source data (e.g., leakage certificate, source model, activity, source strength). These data can be taken by the user, but sample tests should be conducted for evaluation.

In the UK, the medical physicist expert is responsible to verify independently the source calibration before clinical use, as included in the Royal College of Radiologists (RCR) practice guidelines [55].

In some countries such as Spain, it is mandatory [35] to perform independent source strength evaluations, while it is only recommended in most countries.

It should be emphasized, that all national and international protocols and recommendations require that the source strength should always be specified in terms of RAKR (or S_K). This concerns especially the treatment planning systems (TPSS) and the manufac-

turer’s source certificate. The specification of the source strength should include the relative expanded uncertainty (taking into account the class range in prostate case) and the confidence level.

Towards unifying clinical practice within the EU, ESTRO issues recommendations to its medical physicist members in this report. The recommendations made in this document follow closely those of the AAPM [4].

Production, calibration and quality control of the seeds by manufacturer

The manufacturing process of seeds includes various steps until the radiation output parameters of a sealed source can be determined. Thus, the source strength of each individual seed is measured only during the final quality control steps. A set of seed cores is loaded in a radiochemical “batch” process, encapsulated, and afterwards the seeds are classified in different bins, so called “classes”, with consecutive ranges of strength.

In practice, a class range of $\pm 4\%$ is used for ^{125}I , giving an 8% difference in the nominal bin values, which is equivalent to 1-week decay (half-life 59.407 days). Inherently, this binning range is part of the uncertainty on the source RAKR specification for a group of sources (see later in this report). In stock management, there might be seeds available of the same class but from different batches, and a subset of this is sent to the hospital for a specific implant, named “seed order lot” in this report.

For ^{103}Pd seeds, due to the shorter half-life of 16.991 days, narrower class ranges are defined (up to about $\pm 1.5\%$ in width).

For prostate seeds, the manufacturer will not specify the mean source strength for a seed lot but merely the nominal midpoint value of the class range, and refer to the nominal range. If uncertainties are stated in the certificate, their meaning might be unclear (the class range, the individual source RAKR determination, or the total uncertainty), and the confidence level is not always mentioned.

At present, the following ^{125}I seed models are distributed on the European market:

1. Bard Source Tech Medical model STM1251 (Bard Medical, Covington, GA, USA) [46]: this seed model is available as loose seeds in cartridges. Bard also offers a system to link seeds and/or spacers before the implantation procedure (*Source-Link™*). Factory calibrations of air-kerma strength, S_K , by Bard are traceable to the National Institute of Standards and Technology (NIST). Source certificates specify the source strength additionally in terms of A_{app} in mCi. The uncertainty on the assay of sources is stated to be $\pm 5\%$ (coverage factor k not specified), which includes the effect of the binning range ($\pm 4\%$).
2. BEBIG IsoSeed models I25.S06 and I25.S17plus (Eckert & Ziegler BEBIG, Berlin) [48,45]: the designs of the two source models are optimized for different imaging modalities. Both models are available as loose seeds in cartridges or as IsoStrand with 10 seeds or as IsoCord with up to 70 stranded seeds in a sterile cartridge. The source strength is certified as RAKR and the A_{app} is derived from this additionally. BEBIG seeds for prostate are available in 14 classes. The source certificate indicates the range (minimum and maximum) and the mean of the range (nominal midpoint of the class). The uncertainty of the source strength of an individual seed is better than $\pm 4.7\%$ ($k = 2$) according to the nominal midpoint of the class.
3. BEBIG’s seed model I25.S16 is identical in design to I25.S06 with higher source strengths (up to 32 U, e.g., for ophthalmic treatments). This seed model is available in 14 nominal classes. However, different to prostate seeds, seed batches are specified by their mean effective RAKR and selected with a customized range (smaller than the nominal class range and typically $\pm 5\%$).

4. Best seed model 2301 (Best Medical International Inc., Springfield) [48] is available in several European countries through local distributors. The sources can be provided as loose seeds in cartridges, as strands, or preloaded in needles. The source certificate states the nominal class value, in terms of RAKR and apparent activity, with an uncertainty of $\pm 5\%$ (k not specified). The sources are also available with higher RAKR for, e.g., ophthalmic applications.
5. selectSeed model 130.002 (Elekta AB, Stockholm), [45]: This seed model comes in cartridges of up to 100 seeds to be used with the seedSelectron – an automatic seed loader from Elekta. On the source certificate both the RAKR and the apparent activity are specified, with a stated uncertainty of $\pm 4\%$ (k not specified). This uncertainty refers only to the binning range, and does not include any measurement uncertainties.
6. Theragenics model AgX100 (Theragenics Corporation, Buford, Georgia): [45] this seed model is available as loose seeds in cartridges, as strands of up to 6 seeds, or in preloaded needles. Furthermore, Theragenics offers a system that allows individual stranding in conjunction with real-time intraoperative protocols for implantation. The model AgX100 is also available as loose seeds or in pre-loaded plaques for ophthalmic applications. For 2-dimensional applications, seeds are supplied imbedded according to spacing specification in a flexible, absorbable mesh array that can be configured intraoperatively for treatment of tumour bed margins after excision such as sublobar, head and neck therapy, pelvic floor and other treatments. The uncertainty on the RAKR for a batch of seeds is stated to be approximately $\pm 7\%$ (k not specified).

Additionally, one hospital (Erasmus UMC in Rotterdam, The Netherlands) recently started a programme for breast using ^{103}Pd seeds:

7. Theragenics TheraSeed model 200 ^{103}Pd seeds (Theragenics Corporation, Buford, Georgia): [48]. That model is available in the same configurations as AgX100 ^{125}I seeds. The palladium seeds are produced as well in a robust “batch” manufacturing process. A batch contains 200–4000 seeds. Each batch is divided into 7 classes, where the total spread of one class is 2.5% (upper and lower value of the class is $\pm 1.25\%$ of the mean). Each seed in the batch is individually assayed and placed into the appropriate class. All seeds for an order are typically supplied from the same class, but can be taken from up to three classes. This leads to an uncertainty on the RAKR for a lot of seeds stated to be approximately $\pm 7\%$ (k not specified). The source certificate specifies the mean RAKR and range, and the apparent activity mean and range.

Some manufacturers or vendors offer the user a second, independent QC of the seeds before they are sent to the hospital. AAPM [4] discussed this practice and concluded that such third party QC cannot replace the responsibility from the qualified medical physicist from the hospital to measure and verify the source strength of the seeds. GEC-ESTRO ACROP recommendation coincides with those from the AAPM that the hospital medical physicist is responsible for the final QC of all BT sources before use.

Many manufacturers offer to the user the possibility to obtain so-called individually calibrated seeds, further referenced in this document as “factory-calibrated seed”. However, no societal guidelines exist on how the manufacturer should calibrate and document such a seed. Thus, the user should carefully examine the measurement certificate that comes with such factory-calibrated seed regarding measurement procedure, traceability and uncertainty analysis, and ask for additional information whenever this document is unclear or incomplete. A factory-calibrated seed can

be used to clarify potential differences in RAKR determination between the user and the manufacturer (see ‘Recommendations’, paragraph 8c). However, it should be clear that such a seed could never replace a transfer standard traceably calibrated at a primary or secondary standards laboratory, which assures QA independently from the manufacturer’s procedures.

Traceability in calibration, handling of well chambers and related equipment

Traceability in source strength calibration is provided through equipment calibrated in an uninterrupted chain against established metrological standards realizing the requested quantity (the available RAKR (or S_K) standards of national metrology institutes (NMIs), or an absorbed dose-rate to water standard). Traceability to common standards form the base for which the radiotherapy community can communicate and compare outcome results, being an essential aspect of quality and safety of the seed implants. The traceability must account for the source model.

In this section, the traceability chain and the standards available in calibration laboratories are presented together with the requisites and operation of hospital measuring equipment. In Appendix A, the laboratories’ accreditation or corresponding activities and interaction with seeds manufacturers are described and discussed. Also, a discussion on a specific issue in the Λ assessment is included.

Traceability of a quantity at the end-user (hospital) level is achieved through calibration of equipment against a primary or lower level (secondary) standard which is traceable to the primary. Well-type ionization chambers (WICs) are the recommended instruments to determine BT seed strength at hospitals [22,39]. A primary standard is a physical realization of a quantity from first principles (for BT seeds RAKR or S_K , see their definition and close relationship before in this report). The realization is disseminated to low-level standards through calibration (using the same seed model for which the prior standards have determined the RAKR to determine a calibration coefficient N_{RAKR}). For low-energy BT seeds, WICs are the recommended equipment for secondary standards laboratories and end-users. The dissemination to the end-user is in practice obtained through either calibrated WICs or calibrated reference sources.

Traceability can be disseminated either through:

- (i) sending equipment to a primary/secondary laboratory to obtain the calibration coefficient for a WIC, or
- (ii) ordering a seed with a source strength, in terms of RAKR (or S_K), determined and certified at such a laboratory to use in calibrating the own equipment (named “standard source” or “calibrated source”, we will refer it in this report as “reference calibrated source”).

The primary standards for radiation qualities used in clinics start the calibration chain and are developed and maintained by some NMIs while others might offer secondary standards traceable to these. The primary standards are instruments of the highest metrological quality, which realize physical quantities from first principles with stated quantity value and associated measurement uncertainty [24].

BT seeds differ much in interior design and LE-photon emission spectra are substantially affected, even between different source models containing the same radionuclide [48]. Most NMIs consider these differences by determining seed model-specific correction factors for their primary standards. The choice of seed models available for calibration at a given laboratory is based on resources and national requests. Generally, the NMIs expand the number of

seed models calibrated with time. In other cases a type of specific correction factors is not evaluated and this aspect is covered by increasing the uncertainties.

The institutes offering calibration services in Europe for ^{125}I seeds as of December 2018 are included in Appendix I. This list will be maintained and updated at the BRAPHYQS ESTRO website (<http://www.estro.org/about/governance-organisation/committees-activities/gec-estro-braphyqs>).

The 2004 AAPM CLA Report [14] describes the methodology used in the USA, controlled by the AAPM, to guarantee that a seed model fulfils all required quality prerequisites. It reflects the consensus view of AAPM to be used clinically, regarding traceability for end users [62] and the seed design manufacturer constancy. A set of seeds is measured by NIST and ADCLs to establish their traceability and this process is partially repeated annually. Sources that fulfil the prerequisites are included in the IROC (Imaging and Radiation Oncology Core)/Houston-AAPM Brachytherapy Source Registry (http://rpc.mdanderson.org/RPC/BrachySeeds/Source_Registry.htm).

The application of a similar calibration system in Europe is very complicated, and plenty of efforts will be needed to harmonize the interactions among the NMIs, seed manufacturers, and legislations for specific countries. GEC-ESTRO ACROP encourages the promotion of an efficient solution in Europe to guarantee an adequate level of quality. Most of the seeds used in Europe are from manufacturers that also provide seeds to the U.S. and they are therefore included in the IROC/Houston-AAPM Brachytherapy Source Registry. For the exceptional case of seed models manufactured in Europe but not marketed in North-America, the manufacturers should cooperate with European NMIs and calibration labs sending seeds annually to establish and develop an adequate calibration network. This will put standards into practice until European institutions and organizations establish the necessary quality standards and infrastructure.

WICs for use in BT should be air-filled and vented so that ambient conditions inside reach equilibrium with the surroundings with respect to air temperature, pressure and relative humidity. In particular, gas-filled and pressurized WICs of the type used in nuclear medicine should not be used (see, e.g., Ref. [22]) to avoid potential stability problems due to slow leakage of the gas.

In addition to a WIC, an electrometer suitable for the range of currents/integrated charge to be measured is needed. Ionization currents measured with WICs common for the task are typically around a few pA for LDR permanent BT seeds and five to ten times more for LDR temporary seeds (e.g. ophthalmic seeds). The electrometer should either be co-calibrated with the WIC (calibration valid for the WIC + electrometer combination) or separately against a standard for current/charge. A calibrated thermometer, pressure gauge and hygrometer are also required.

WICs are comparatively large ionization chambers (typical air volumes of 50–250 cm³) and generally considered as robust instruments, data on their long-term stability have been reported, e.g., [9]. Recalibration every 24 months is recommended and aligned with requirements for external-beam dosimetry instrumentation [39,60]. Additional recalibration should be done immediately after doubts on its performance or after repair. Constancy of the equipment should be tested regularly. In the case of BT seeds it is important that the seed-insert is also checked, since the insert determines the position of the source inside the chamber well and the signal and hence calibration coefficient is dependent upon that location.

A redundant test is obtained by measuring the same seed with two fully independent systems (WIC + insert). Once established, the ratio of currents or integrated charges between the two systems should vary with time within the uncertainty of their measurements [8]. The constancy of electrometer, thermometer and pressure gauge must also be regularly checked. The constancy of

a WIC can also be checked through use of a long-lived source (e.g., a ^{137}Cs or ^{90}Sr source) or through linac or kV-beam irradiation in a well-defined geometric setup [60,20], however the associated uncertainty can be an issue. The latter alternatives do not check the BT source insert which would hence have to be checked separately using, e.g., a ruler. For different practical reasons, the most adequate redundant system is to have two independent WIC + insert and electrometer.

As the WICs are vented to ambient air, measurements need to be corrected for climatic conditions with the ratio of air temperatures and pressures with respect to the reference conditions used at calibration $k_{TP} = (T \times p_0)/(T_0 \times p)$ (T in K). Due to the low energy of seeds, an extra correction factor for air pressure may be needed. High altitude sites with respect to the calibration laboratories must take into account this correction. Griffin et al. [19] provided corrections for the Standard Imaging HDR1000 Plus well chamber, with specific coefficients according to the radionuclide (^{125}I or ^{103}Pd) and the seed model. In addition, a hygrometer should be used to verify that the WIC is used in conditions for which humidity effects can be neglected (30%–75%).

For the PTW well chambers, Tornero-Lopez et al. [58] proposed a correction, different from Griffin et al., based on an expression with specific coefficients. It worked very well for the case of the new PTW SourceCheck 4pi (model 33005) but not for the widely used old SourceCheck (model 34051), because the specific correction coefficients are device dependent [59]. When a medical physicist is not confident with the application of this correction, the calibration of the WIC should be performed directly on site with a calibrated reference source, because of the uncertainties.

Due to the comparatively large air volume of WICs, it takes time for the chamber air to reach equilibrium with the surrounding air (see Fig. 3.5, in [60]). A WIC should hence be placed in the room where measurements are to be performed hours in advance and further, the thermometer to determine air temperature is best placed inside the chamber well.

A WIC calibration is performed under well-defined conditions (WIC insert, temperature, pressure of air etc.). The resulting calibration coefficient is strictly valid under these conditions. The calibration certificate must hence provide detailed information on these so they can be reproduced by end-user. Details that should be specified on a WIC calibration certificate:

- Information on the WIC (manufacturer, model, serial number). If the calibration is for the WIC alone or in combination with an electrometer (WIC + EM) (if so the manufacturer, model and serial number of the EM also needs to be specified too).
- Information on operating voltage and its polarity (both in WIC and WIC + EM case).
- The calibration coefficient, its units, and uncertainty including confidence interval.
- The seed model for which the calibration coefficient is valid.
- Information on the reference conditions of air temperature and pressure under which the calibration coefficient is valid (note that the reference temperature is 20 °C in Europe while it is 22 °C in North America). Information on the range of relative humidity for which it is valid.
- Information must be given about what air density correction has been used, and the temperature and pressure values, together with the humidity range, for which the calibration has been made.
- Information on traceability (i.e., to which primary standard) and, if relevant, information on the secondary standard step, and data on the secondary standard (WIC model, serial number, date of calibration).
- Information on the source insert used and the height within the WIC where the seed is positioned.

- Information about the BT source/seed used in the calibration (manufacturer, model, source strength at time of calibration).

The AAPM and ESTRO recommend [45] the NNDC website (<http://www.nndc.bnl.gov/index.jsp>) as the reference for BT radionuclide half-life ($T_{1/2}$) values. The current values are: 59.407 (10) days, 16.991(34) days and 9.689(1) days for ^{125}I , ^{103}Pd and ^{131}Cs , respectively.

Considerations in grouped seed assay. Status of available equipment and accessories

As commented before in this report, seed assays shall be performed by the hospital physicist using equipment with calibration independent from the manufacturer to compare with the manufacturer's certificate.

Order lot sizes for a prostate case range typically between 40 and 100 seeds and for ophthalmic case from 5 to 24 seeds. While ophthalmic seeds are distributed as loose seeds for temporary implantation and will be inserted in special holders (usually COMS-applicators), prostate seeds are implanted permanently, individually as either loose seeds, or linked as source chains. There are different link technologies: seeds embedded in bio-absorbable material as strands or just coupled by spacers with special design. Seed strands are delivered customized, or can be cut to length, or even built up from components just prior to implantation. Different strand materials and seed models used in Europe have been described before in this report.

In treatment planning, the source strength is represented by the class mean value. Typically, TPSs are designed for the use of one RAKR value for all the implanted seeds. To verify the delivered RAKR-class, a spot check can be performed on sequentially measured seeds or by assaying a group of seeds at once with a well-type chamber and a dedicated chamber insert. Caution is advised to assure the appropriate calibration for the given seed model and seed holder. Sequential individual measurements are superior to grouped checks because of lower uncertainty. For measurements of grouped seeds, special inserts are available. However, the quantity mean source strength is not in the scope of accredited labs and thus not offered by calibration service. Performing measurements on grouped seeds and their uncertainty analysis are solely the responsibility of the clinical medical physicist.

There are different accessories/inserts offered by the manufacturers of well-type chambers to perform an assay of single or grouped seeds, below some examples are given. Hereby, the number of seeds can be customized, and strands can be inserted in different lengths, typically up to 10 seeds.

Standard Imaging (Standard Imaging, Middleton, USA) markets the well-type chamber HDR1000 Plus. Besides the single seed holder (model 70043), a strand holder (model 70023) for 10 seeds is offered, where 5 seeds are shielded, and the strand must be turned to measure the whole configuration. For the RapidStrand, a typical correction factor of 1.15 to the calibration chamber coefficient, here referred to as "correspondence factor", was stated in the well chamber manual (Standard Imaging, Middleton, WI, USA). Although RapidStrand is not available anymore, this methodology can be applied to other strand models with a maximum of 10 seeds. The HDR1000Plus well chamber has a specific response profile which is uniform just at the central 1 cm, then measurement is done with seeds outside this flat response area. The chamber's response profile must be investigated upfront and corrections included in the uncertainty budget.

A commonly used chamber in Europe is the SourceCheck model 34051 (PTW, Germany) though not available on the market anymore. This well chamber has a horizontal, parallel plate configura-

tion and the flat response area is around 9–10 cm. PTW provides an insert to be set into the chamber body, designed for up to 10 seeds. The assay is performed with all seeds fully within the flat response area. PTW provides a specific correspondence factor for this setup and insert. Also for this chamber, an insert was developed for loose seeds. In this set-up, the chamber was embedded in backscatter material from both sides and it was applied for instance to the selectSeed of Elekta [43].

PTW has developed the well chamber SourceCheck 4pi (model 33005), with vertical set-up. For this chamber, specific inserts for individual or stranded seeds are provided. An insert has been developed to measure grouped loose seeds. It is easily applicable as well to stranded ones [7].

In general, for the WICs, as the chamber response in case of a group of seeds differs significantly with respect to single seed measurements, a correspondence factor is needed to correct for positioning and shielding effects. Although there are values published in the literature or in the manual provided by the manufacturer, the user should obtain these values himself and estimate the uncertainties. In principle, there are two methods to do this. Both or just one are applicable according to the strand characteristics. One option (I) is to measure the grouped seeds in the specific holder and additionally each seed individually in the insert used during the WIC calibration. Another option (II) is to measure just 1 seed in each position of the grouped seed holder and comparing it with the calibration geometry value, for this method spacers are needed to fill in the empty seeds positions.

In case of stranded seeds, typically option I is used. Once the whole strand is assayed, the user can cut it to isolated seeds and measures with the calibration insert for single seeds. A practical problem exists with stranded seeds when the resulting external diameter is too thick for a single seed insert, as the BEBIG case; it is not convenient for the user to remove the plastic because the source encapsulation might be damaged leading to a high risk of contamination. To solve this issue, BEBIG e.g. provides upon request a set of loose seeds of the same class in a separate container, allowing to perform the assay with this set of seeds instead of using a cut piece of strand.

In the determination of the calibration factor and the associated uncertainty in the case of holders allowing several seeds simultaneously, the reference Tornero-López et al. [57] may be of interest to the readers of this report.

Loose seeds in sterilized cartridges

In prostate seed applications, there are techniques where loose seeds are provided in sterilized cartridges to use in manual or automatic afterloader systems. This concerns Mick[®], seedSelectron[®] (Elekta) and Quicklink[®] (Bard) cartridges. These systems allow the modification of needle composition (seed and spacers) once all needles are inserted prior to seed insertion. [33,61].

If a user cannot extract the seeds from the sterilized cartridge for assaying without compromising the sterility of the remaining seeds in the cartridge, it is recommended to order an extra container with not necessary sterilized seeds to perform the assay. The manufacturer must certify that both seed groups, sterile and non-sterile, are of the same seed class and order lot as those used for treatment.

Currently there is only one commercially available robotic seed loader, the seedSelectron (Elekta AB, Stockholm, Sweden). Some practical considerations for this treatment unit are described below, while more detailed information is available [48].

The seedSelectron builds in real-time any planned combination of seeds and spacers and then positions them automatically into implanted needles using a digitally motorized and monitored drive-wire.

Concerning the source strength verification, the seedSelectron has a built-in array of 16 diodes for detecting the presence or absence of ^{125}I seeds when creating the seed/spacer train. The diode array can be configured to further serve as an indication of source strength of each individual ^{125}I seed included in the train. Seeds and spacers are placed in the compose element, forming a train to be delivered through a needle. Radiation is detected by 16 PIN-type (P-type, Intrinsic, and N-type material) diodes, detecting light emitted by a scintillator layer. Collimators are used to limit the detection from the well-separated seed positions. First, a calibration seed has to be measured in order to compare the strength of the other seeds from the same batch. The strength of the seeds, measured by the diodes, will be compared to the strength of the calibration seed. Deviations from that strength were initially indicated using three different colours: green (within 10%), yellow (between 10% and 20%), and red (more than 20%). Currently only two colour ranges are defined: green and red (for reasons explained in the next paragraph). The tolerance ranges can be changed to fulfil the user preferences. There are two options for the calibration of the radiation sensors of the seedSelectron: using a special reference seed delivered by the manufacturer together with the separate calibration certificate, or a seed from a treatment cartridge. The calibration seed cannot be used for patient treatment.

Due to LDR radiation, seeds need to be positioned close to the detector. This makes the system sensitive to diode-seed positioning uncertainties in the compose element (built train) and position of the compose element in the seedSelectron. The presence of the other seeds in the compose element also slightly influences the measured source strength. Consequently, the seedSelectron radiation sensors (diode array) cannot serve as an accurate measurement device for source strength. From a practical point of view, the detector system can confirm the desired combination of active and inactive elements (i.e., seeds or spacers) and detect the seeds with unusually large strength deviation from the expected value.

The source assay procedure for seedSelectron users has not been established in any recommendations, and there is a wide difference in procedures, applied by different institutions: from centres not assaying any seeds to other centres assaying the recommended 5 seeds by AAPM [4], the most frequent scenario being the assaying of just 1–2 seeds. A solution to this is to ask the manufacturer to supply a container with the required number of seeds to perform the assay together with a document in which the manufacturer states that this group of seeds belongs to the same seed class and order lot as those in the cartridge used for the patient [43]. Then the assay can be performed in advance of the implant and all seeds can be measured.

Assay tolerance at hospital level

In the 2008 report by Butler et al. [4], the AAPM stated the quantities of seeds to be assayed by the end-user medical physicist, being the minimum number 5% or 5 seeds. In these AAPM recommendations, the actions to be taken when the value assayed by the medical physicist is compared with the manufacturer's source strength certificate are also included.

In case of individual sources, if the difference is $\leq 6\%$ no action is needed, but if it resulted in $>6\%$ the radiation oncologist should be consulted regarding the use of this source (it is dependent on the radionuclide, intended target, source packaging, and the availability of other sources). In case of seed order lots <10 seeds, the 6% tolerance value is reduced to 5%.

In case of a set of sources assay, if the difference of the mean of the set with respect to manufacturer nominal value exceeds 5%, the sample size should be increased if possible. If the difference is confirmed, it must be investigated with the manufacturer and it is

required to consult the radiation oncologist regarding whether to use the measured source strength or to average with the manufacturer's value. The medical physicist will point out to the radiation oncologist the consequences of proceeding with the implant using the estimated source strength.

These recommendations have been followed by clinical medical physicists and have been endorsed by professional organizations. However, the statistical significance and the related dosimetric impacts of these AAPM recommendations have not been systematically evaluated. In Appendix B, a more detailed uncertainty analysis has been performed trying to support the AAPM recommendations of 5% or 5 seeds. In this analysis, some assumptions have been made due to the limited knowledge of a realistic RAKR distribution in each class for each manufacturer. It will be matter for future research.

GEC-ESTRO ACROP recommendations

In this report, the strength of the recommendation will be classified by adopting the terminology typically used in AAPM guidelines:

- **MUST or MUST NOT:** used to indicate that adherence to the recommendation is considered necessary to conform to this practice guideline
- **SHOULD OR SHOULD NOT:** used to indicate a prudent practice for which exceptions may occasionally be made in appropriate circumstances

With the main aim being a high quality and safe LDR-LE seed implant and taking into account the clinical practice scenario, GEC-ESTRO ACROP establishes the following recommendations.

1. It is the responsibility of the hospital medical physicist to assay BT seeds. Administrators must facilitate the required resources. The assay must be performed in advance of the clinical procedure (i.e., the BT implant) to assure an early enough reaction if the assay indicates a discrepancy with the manufacturer's certificate.
2. The recommended equipment is a WIC with source-holder insert (WIC&I), an electrometer, a barometer, and a thermometer. All devices must be calibrated at least every 24 months by an accredited laboratory or an NMI. Moreover the availability of a hygrometer is recommended, in this case the accuracy can also be lower (10%) and the calibration interval can be wider. Alternatively, the WIC&I can be calibrated by the physicist using a reference calibrated seed of the given model from an accredited laboratory or an NMI, also with a minimum of 24 month' frequency.
3. A convenient system to check the stability of the WIC must be available. Recommended equipment is another WIC&I in analogy with the common practice used for linac-based external-beam radiotherapy dosimetry.
4. According to the local air-pressure, specific additional pressure corrections must be evaluated and applied. If these are not well established, calibration on site with a reference calibrated source is recommended.
5. For temporary implants (e.g., ophthalmic BT), all N seeds to be implanted must be assayed.
6. For volumetric implants with a larger number of N seeds (e.g., permanent prostate BT), the assay is performed through statistical inference using a sample of n from the N seeds used for the patient (see Appendix II for the determination of n).
7. The n seeds for statistical inference assaying must pertain to the seed class and order lot used for the patient. For these cases not possible due to sterilization conditions, the physicist will request a separate vial of seeds from the manufacturer. The

manufacturer must certify that these seeds are from the same seed class and order lot as the sterile seeds in the cartridges to be used for the patient.

8. When possible, the seeds should be measured individually. If the user has confidence with seeds dispersion, grouped measurements can be applied because of practical efficiency reasons (at the end, all seeds are used together in the implant and RAKR is averaged in both: input value and TPS used value). The aim of the assay is to evaluate the mean reference air-kerma rate of the seeds ${}_{user}RAKR_{mean}$. Specific inserts are used if seeds are assayed individually or as a group (for positioning the seeds centrally in the well chamber). The “correspondence factor” of these inserts must be established by the hospital physicist estimating the associated uncertainty.
9. Because of the lack of knowledge of realistic seed class distributions, the current AAPM statistical inference recommendations are adopted. Then, at least $n = 5$ seeds must be assayed. The measured ${}_{user}RAKR_{mean}$ value must be compared with the stated value on the manufacturer certificate ${}_{manu}RAKR$ according to:

$$\frac{|{}_{manu}RAKR - {}_{user}RAKR_{mean}|}{{}_{user}RAKR_{mean}} \times 100\% \quad (2)$$

- a) If ${}_{manu}RAKR$ and ${}_{user}RAKR_{mean}$ are within the established tolerance of 5%, either value can be introduced into the BT TPS.
 - b) If the difference exceeds the tolerance, the measurements should be redone and checked by another qualified person identified in advance. If feasible, the physicist should extend the assay with 5 additional seeds to validate the result. If the discrepancy is confirmed or it is not possible to measure another set of seeds, the discrepancy should be communicated and clarified with the manufacturer. The physicist and radiation oncologist responsible for the implant must decide together whether or not to proceed with the implant.
 - c) If reasonable, a factory calibrated seed should be requested to the manufacturer with the corresponding certificate. This seed should be carefully measured in a reference instrument with adequate traceability, and all measurement details must be included in the calibration certificate (measurement procedure, traceability and uncertainty) being open for additional information. An efficient dialogue should be promoted commonly to solve potential assay discrepancies.
10. Regarding the seedSelectron, the diodes do not have sufficient accuracy, and a set of loose seeds must be assayed as described above.
 11. The manufacturer's calibration certificate must include ${}_{manu}RAKR$, the associated uncertainty and coverage factor of this value, the date and time associated with the ${}_{manu}RAKR$ value, the date and time format (e.g., ISO 8601), and information about traceability to an RAKR-standard. If due to regulations or administrative purposes the activity (apparent and/or contained) is included on the manufacturer calibration certificate, the assumed conversion factor(s) regarding RAKR must be explicitly stated.
 12. This WP-18, BRAPHYQS, and GEC-ESTRO ACROP encourage promotion of an efficient solution in Europe to monitor and assure seed design constancy. Most of the seeds used in Europe are from manufacturers that also provide seeds to North America and are therefore included in the IROC-AAPM Brachytherapy Source Registry. For the exceptional case where seeds are made only for the European market, European seed manufacturers should send at least 3 seeds on a yearly basis to an appropriate NMI for adequate checks. It should start by January 1 2020, until European institutions and organizations establish the necessary quality standards and infrastructure.

13. The authors of this report recommend carefully consider the conception of Λ_{WAFAC} , in case of calibration traceable to NIST according to [Appendix A](#), as it discloses the real meaning of Λ , being a source specific constant independent of a specific primary standard (see AI.4 for the details). Λ_{WAFAC} is specific of the NIST primary standard because it had combined Λ with a volume to point detector conversion of the WAFAC standard chamber. Unfortunately, a volume to point detector conversion based on point sources already performed by NIST was overlooked in many cases (see details in AI.4). Published Λ_{WAFAC} values therefore need to be re-evaluated if this fact has been considered or not. Furthermore, a practice established in the U.S. should not be simply assigned to NMIs and primary standards in other countries. The realization of a quantity according to its definition (as a point like quantity) is part of the sovereign function of a NMI. Dosimetric investigators willing to recommend a correction for a specific primary standard should not do this without contacting the corresponding institute to ensure the correctness of their approach.

Conflict of interest statement

Michael Andr assy is an employee of Eckert & Ziegler BEBIG who contributed to the guideline as a consultant.

Yury Niatsetski is an employee of Elekta who contributed to the guideline as a consultant.

The rest of the authors declare that they have no competing interests or any financial or personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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WP-18 is a group where all European seed calibration laboratories and seed providers are included together with BRAPHYQS. This whole group will work on different projects based upon open challenges already commented in this report. Some of them are the primary calibration harmonization between laboratories, uncertainties according to specific manufacturer procedures and seed manufacturer constancy control within Europe.

Appendix A and B. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2019.02.008>.

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Further Reading: Appendix I and II

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