SABR in clinical trials: What quality assurance (QA) is required and how can it be done?

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Abstract
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Disciplines
Engineering | Science and Technology Studies

Publication Details

This journal article is available at Research Online: https://ro.uow.edu.au/eispapers1/2830
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To cite this article: T Kron and N Hardcastle 2019 J. Phys.: Conf. Ser. 1154 012014

View the article online for updates and enhancements.
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Abstract. Stereotactic Ablative Body Radiotherapy (SABR) has become widely used radiotherapy treatment modality for many indications ranging from early stage disease to an oligometastatic setting. All this combines the use of virtually all technological advances that characterise modern radiotherapy from small conformal fields to intensity modulation and explicit accounting for motion. However, given its novelty, clinical evidence for SABR is still emerging and many clinical trails include SABR as the intervention to define (eg in dose or fractionation defining studies) or to test against other treatment modalities. In any case, physical quality assurance (QA) must be an essential aspect of the trial to ensure that SABR is delivered accurately and in a comparable fashion in radiotherapy centres participating in the trial. The present paper tries to explore the balance between the QA cost and benefit for trial conduct in terms of patient numbers and timely completion of the trial.

1. Introduction
Stereotactic Ablative Body Radiotherapy (SABR) or Stereotactic Body Radiation Therapy (SBRT) as it is called in North America has quickly developed into a widely used treatment modality for a number of cancers [1-3]). However, high-level clinical evidence is only slowly emerging and there is general agreement that more clinical trials are required to define the intervention of SABR in terms of dose, fractionation and delivery technique as well as compare it with other treatment modalities and explore potential late effects [4]. Given the stark contrast in modalities such as surgery and SABR for early stage lung disease it is also difficult to recruit patients to these trials as equipoise may neither exist for an individual patient nor their caring clinician [5-8].

It is difficult to demand evidence for many technology-driven changes as has been discussed extensively in the context of IMRT and proton radiotherapy [9]. However, high-level evidence with clinical endpoints is desirable for the introduction of new technology and governments; regulatory authorities and health insurance companies usually demand it. In this context high-level evidence is defined as the outcomes of at least one randomised controlled trial. In practice, often not only the effectiveness of the new intervention is considered but also the resource requirements such as time and cost. A standard decision-making matrix is shown in figure 1. It is interesting to note that the quality assurance activities for clinical trials can help to identify some of the ‘other factors’ considered in the two blue diagonal fields. Robustness against unintended variations, complexity, training requirements and cost would be some of these factors.
Some additional issues are also worth consideration when looking for clinical evidence in a technology driven field like radiation oncology:

- Technology changes quickly and clinical endpoint may take a long time to be tested. As such, the results of a clinical trial may refer to old technology by the time they are mature.
- Implementation of technology and techniques may vary more amongst centres participating in a trial that tests new approaches for which no clinical guidelines exist.
- There is often a learning curve with new techniques; trials testing them may not reflect the optimum implementation at the early stage of a trial.

All this leads to an increased need to provide stringent quality assurance procedures for such trials. The current paper explores how this can be done in the context of SABR.

**Figure 1.** Typical scheme to introduce new technologies or techniques (‘interventions’).

### 2. Technical challenges for SABR

The concept of SABR is derived from intracranial stereotactic procedures where high radiation doses are given to small lesions in a very conformal fashion since more than 50 years using mostly rigid frames attached to the patient’s skull to ensure accurate field localisation. However, compared to intracranial delivery, SABR is considerably more difficult as the body consists of heterogeneous, non-rigid materials, and the target is likely to move against the fixed reference frame typically used for image guidance [10, 11]. Figure 2 shows an illustration of typical SABR scenarios. Image guidance has largely replaced physical frames as the stereotactic ‘frame of reference.

**Figure 2.** Schematic drawing of two SABR scenarios which may require different technical solutions: a) the original paradigm where a target is embedded in a large normal organ, typically a parallel organised radiobiological structure. Lung and liver are examples for this. b) a more complex SABR scenario consists of critical structures being either in close proximity or even enclosed by the target. Vertebral and prostate SABR treatments would be example for this.
Several clinical trials using scenario a in figure 2 are currently closed to accrual either because they are completed, or they failed to recruit. While the concept of SABR was pioneered in Scandinavia, [12, 13] it was the phase I trial by Timmerman et al performed in a single institution that inspired a paradigm shift in radiation oncology [14, 15]. Not surprisingly, the need for quality assurance in stereotactic body radiotherapy was identified almost immediately [16].

3. Physical QA for trials and their impact

The impact on clinical outcomes and thus clinical trial findings of quality assurance has been documented in several settings [17, 18]. In several circumstances the lack of adequate quality assurance may have prevented the trial from answering the trial question [19-21] or has affected clinical outcomes [22, 23]. This leads to the primary objective of trial QA to ensure that the trial is best positioned to answer the trial question. It is important to note that trial QA therefore does NOT ensure safe patient treatment in itself but aims to support the investigator in addressing the hypothesis of the trial. Figure 3 illustrates the resulting dilemma for a trial chair: optimising accrual by making it as easy as possible to contribute to the trial or tightening the quality criteria to standardise the trial and improve data quality.

A different consideration though is that high quality data generally reduces the quantity of data required to answer a question and thus can reduce the number of patients (and therefore the cost and time) required for a trial [20]. This has been elegantly demonstrated by Pettersen et al in 2008 [24]. When considering how few events determine the outcome of a trial this need for stringent quality control of data becomes obvious.

Trials that employ high-end technology such as SABR trials are particularly vulnerable to technological issues and careful consideration must be given to QA tools employed. In general trials use several tools to ensure quality data from a technology perspective [25]. Of particular relevance are:

- Credentialing of centres prior to being activated for accrual – this typically includes a benchmarking planning study and dosimetric audits
- Review of treatment plans for individual patients

The extreme hypofractionation in SABR relies on severe restrictions of dose to normal tissues utilising high-end technology and techniques. Their appropriate use requires generally stringent QA measures. Given that small field dosimetry is more complicated than dosimetry for conventional radiotherapy, dosimetric audits become particularly important and Clark et al provide a good summary of this in the recent literature [26]. Small field dosimetry was also identified as one issue in a recent study on credentialing for a SABR trial by our group [27]. Dosimetric audits for small fields are also offered by the IROC centre in Houston which also published a very useful compilation of small field output data [28]. The problem of dosimetry in small fields gets even more complicated if flattening filter free
(FFF) beams are used where spectral variations and high dose rate can complicate dosimetry further [29].

Furthermore, heterogeneities have posed issues for trial dosimetry [30]. It is interesting to note that retrospective analysis of the dose calculation algorithms in RTOG0236 led to an adjustment of the dose per fraction in the three fractions treatments from 20Gy to 18Gy to account for the lack of adequate inhomogeneity corrections in the dose calculation [31]. This has been shown to be problematic by our group and has also been identified also by the Australian Clinical Dosimetry Service (ACDS), a national dosimetric audit network [27, 32]. A number of dosimetric audits for SABR in lung cancer have attempted to address this [26, 27, 33]. More modern dose calculation algorithms such as Monte Carlo and use of the linear Boltzman equation introduce further complexity with the concept of dose to medium. Variations in dose reporting can lead to significant differences in delivered doses between centres that use dose to medium and those who use more traditional algorithms which report dose to water, in particular to bony targets [34, 35].

In the context of clinical trials dosimetric audits can be organised in different ways. They can be centrally organised such as in Australia [36] and North America [37, 38] or use a round robin approach where centres audit each other [39] The advantage of the centrally organised audits is that they are usually associated with a National Standard Laboratory, which ensures traceability of dose. Given the workload these centres also usually operate remotely using mail-out phantoms. Round Robins are more likely to include site visits that have the advantage that they can include education and other observations that are useful in the context of clinical trials [27, 40].

In the context of SABR also motion management and image guidance are important. Motion management audits are part of several IROC audits for liver and lung SABR [41, 42] and they have also been used in UK [43] and Australia [27, 44]. Similarly, image guidance is an essential aspect of trial QA and several methods have been reported in the literature [45-50].

4. Conclusion
There is no perfect quality assurance program for SABR, in particular given the wide variety and increasing number of targets treated. However, there is consensus that participation in clinical trials for SABR does require some independent quality assurance activities to ensure technology and techniques are used in a consistent way across all participating centres. As most clinical trials to date are considering SABR of lung lesions, heterogeneities, motion and small fields are key aspects of the checks. However, given the move of SABR applications to targets very close to critical structures as illustrated in figure 2, also the steepness of dose fall off and location of the dose gradient and as such image guidance are becoming increasingly important. As SABR trials start to involve more than one lesion in lung, liver and brain it will be interesting to see how audits for these scenarios will be developed in the future.

5. Acknowledgments
We would like to acknowledge the financial support of the Gross Foundation for our SABR program.

6. References
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