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MedPeer Publisher
Abbreviated Key Title: MedPeer
ISSN : 3066-2737
homepage: https://www.medpeerpublishers.com

Sequential boost versus simultaneous integrated boost after breast radiotherapy: real-world practice, data completeness and exploratory outcomes in a single-centre cohort of 572 patients

DOI: 10.70780/medpeer.000QGYD

AUTHOR AND AFFILIATION

Salma Ichou [1, 2,3], Karima Nouni [1, 2,3] , Amine Lachgar [1, 2,3], Hanan ElKacemi [1, 2,3], Tayeb Kebdani [1, 2,3] , Khalid Hassouni [1, 2,3]

[1] Department of Radiation Therapy, National Institute of Oncology, Rabat, Morocco
[2] Faculty of Medicine and Pharmacy of Rabat, Morocco
[3] University Mohammed V, Rabat, Morocco

Corresponding author: Salma Ichou.

ABSTRACT

Background. After breast-conserving surgery, the tumour-bed boost can be delivered sequentially or as a simultaneous integrated boost (SIB). Randomised trials support SIB, but real-world data from centres with limited linear accelerator capacity are scarce, and routine databases may not capture the outcomes needed for comparison. We described the use of both techniques in a reference centre, assessed the completeness of routinely recorded data, and explored acute toxicity and overall treatment time.
Methods. Retrospective single-centre study of a radiotherapy department database (2020–2023), reported according to STROBE. Patients with a recorded boost technique were included. Institutional schedules were 42 Gy in 15 fractions followed by a sequential boost of 11.2 Gy in 4 fractions, or 40.05 Gy in 15 fractions with a SIB of 48 Gy in 15 fractions. Outcomes were reported acute toxicity, CTCAE radiodermatitis grade and overall treatment time; completeness was assessed for each variable and group. Biologically equivalent doses (EQD2) of both schedules were calculated. The analysis was descriptive.
Results. Of 572 patients, 501 (87.6%) received a sequential boost and 71 (12.4%) a SIB. Reported acute toxicity was available for more than 97% of patients in both groups, and was reported in 13.5% (sequential) versus 1.4% (SIB) of them, but radiodermatitis grade was recorded for only 16.0% and 1.4% of patients, and overall treatment time for 9.8% and 81.7%, respectively. Median recorded overall treatment time was 21 days in both groups, below the minimum expected for the sequential schedule (25 days), indicating incomplete recording of end dates. The doses recorded for SIB patients (42 Gy to the breast, boost of 11.2 Gy) were those of the sequential schedule, suggesting misclassification of the technique,

and 55% of patients had a mastectomy. On the protocol schedules, the sequential schedule had a higher EQD2 to both the whole breast and the tumour bed.
Conclusion. Sequential boost dominated practice, and routinely recorded data did not allow a valid comparison of toxicity or treatment duration between techniques. We propose a minimum dataset for prospective recording before comparative conclusions can be drawn.

KEYWORDS

breast cancer; radiotherapy; tumour-bed boost; simultaneous integrated boost; radiodermatitis; overall treatment time; data quality; real-world data

MAIN ARTICLE

1. INTRODUCTION

Breast-conserving surgery followed by whole-breast irradiation is the standard of care for most patients with early breast cancer, and adjuvant radiotherapy reduces both the risk of local recurrence and breast cancer mortality [1]. Adding a boost to the tumour bed further improves local control. In the EORTC 22881-10882 trial, a 16 Gy boost reduced the 20-year cumulative incidence of ipsilateral breast tumour recurrence from 16.4% to 12.0%, with the largest absolute benefit in young patients, at the cost of more moderate to severe fibrosis [2,3].

Two strategies are used to deliver the boost. The sequential boost is given after whole-breast irradiation, in one or several additional fractions, and therefore lengthens the overall treatment time. The simultaneous integrated boost (SIB) is delivered during whole-breast irradiation by giving a higher dose per fraction to the tumour bed, so that the whole treatment is completed in a single plan with fewer visits. The rise of hypofractionated schedules, validated by the START B, Canadian and FAST-Forward trials [4–6], has strengthened the appeal of SIB. Randomised evidence is now available: IMPORT HIGH showed that SIB was safe and reduced the number of patient visits [7], the IMRT-MC2 trial showed that intensity-modulated SIB was non-inferior to a sequential boost for local control and cosmesis while shortening treatment [8], and the NRG/RTOG 1005 trial found that a three-week hypofractionated course with a concurrent boost was non-inferior to conventional treatment with a sequential boost in high-risk patients [9]. These issues are especially relevant where linear accelerator capacity is limited and patients may live far from the treatment centre.

The acute skin tolerance of SIB nevertheless remains a concern, since the higher dose per fraction in the boost volume may theoretically increase radiodermatitis, and SIB requires more complex planning, usually with intensity modulation. Before such questions can be addressed with institutional data, the quality of routinely recorded information must be known. The objectives of this study, conducted in a single reference centre treating a large number of breast

cancers, were (i) to describe the use of sequential boost and SIB, (ii) to assess the completeness and consistency of the routinely recorded variables needed to compare them, and (iii) to explore acute skin toxicity and overall treatment time in each group.

2. MATERIALS AND METHODS

2.1 Study design and setting

This was a retrospective, single-centre, descriptive study based on the clinical database of the radiotherapy department of National institute of Oncology of Rabat, covering the period 2020–2023. It is reported in accordance with the STROBE statement for observational studies [10].

2.2 Population

We included patients who received breast or chest-wall radiotherapy for breast cancer and whose boost technique was recorded ("sequential" or "SIB"). Patients with no information on the boost technique were not analysed. The selection process is shown in Figure 1. Of the 572 patients analysed, 316 (55.2%) were treated after mastectomy (268 in the sequential group and 48 in the SIB group), 251 (43.9%) after breast-conserving surgery, and the type of surgery was mixed or not recorded in 5. The database does not specify what the recorded "boost" corresponded to after mastectomy: a boost was recorded as "yes" in only 4 of the 316 mastectomy patients (3 sequential, 1 SIB), as "no" in 289 and was not recorded in 23. The technique field ("sequential" or "SIB") therefore appears to have been completed irrespective of whether a boost was actually delivered.

2.3 Radiotherapy schedules

All patients were treated with a moderately hypofractionated schedule according to the institutional protocol (Table 1). In the sequential group, the breast or chest wall received 42 Gy in 15 fractions of 2.8 Gy, followed by a sequential tumour-bed boost of 11.2 Gy in 4 fractions of 2.8 Gy. In the SIB group, the breast received 40.05 Gy in 15 fractions (2.67 Gy per fraction) with a simultaneous integrated boost to the tumour bed of 48 Gy in 15 fractions (3.2 Gy per fraction), the boost dose tested in the 48 Gy arm of IMPORT HIGH [7]. All patients with a recorded planning technique (571 of 572) were planned with three-dimensional conformal radiotherapy (3D-CRT), including those in the SIB group; no IMRT or VMAT plans were recorded.

To compare the biological intensity of the two schedules, equivalent doses in 2 Gy fractions (EQD2) were calculated with the linear-quadratic model, using an α/β ratio of 10 Gy for acute skin reactions and of 3.5 Gy for tumour control and late normal-tissue effects [12]. No correction was made for overall treatment time.

Table 1. Radiotherapy schedules by boost technique and calculated equivalent doses in 2 Gy fractions (EQD2).

Technique / volume	Physical dose	Dose per fraction	Fractions	EQD2, α/β = 10 Gy	EQD2, α/β = 3.5 Gy
Sequential – whole breast / chest wall	42 Gy	2.8 Gy	15	44.8 Gy	48.1 Gy
Sequential – tumour bed (cumulative)	42 + 11.2 = 53.2 Gy	2.8 Gy	15 + 4 = 19	56.7 Gy	60.9 Gy
SIB – whole breast	40.05 Gy	2.67 Gy	15	42.3 Gy	44.9 Gy
SIB – tumour bed	48 Gy	3.2 Gy	15	52.8 Gy	58.5 Gy

EQD2 = D × (d + α/β) / (2 + α/β), where D is the total dose and d the dose per fraction; no correction for overall treatment time. SIB, simultaneous integrated boost.

2.4 Variables and definitions

The extracted variables were boost technique, recorded boost dose (Gy), year of treatment, reported acute toxicity (any toxicity recorded in the database, without standardised grading), radiodermatitis grade according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [11], treatment interruption, and overall treatment time. Overall treatment time was defined as the number of calendar days from the first to the last radiotherapy session, both included. On this basis, and assuming five fractions per week without interruption, the minimum expected overall treatment time was 19 days for the 15-fraction SIB schedule and 25 days for the 19-fraction sequential schedule. Individual fractionation was not extracted from the database; the schedules described above are those of the institutional protocol. The patient characteristics available in the database were age, type of surgery, pathological pT and pN stage, systemic treatments (endocrine therapy), regional nodal irradiation and planning technique. Body mass index was not recorded. pT and pN stages were harmonised from free-text entries (ypT/ypN and sentinel-node entries were pooled with pT/pN).

Completeness was defined, for each variable and group, as the proportion of patients with a non-missing value. Consistency was assessed by comparing recorded values with the expected values of the institutional protocol (boost dose, minimum overall treatment time).

2.5 Statistical analysis

The analysis was purely descriptive. Categorical variables are expressed as counts and percentages, and quantitative variables as medians with interquartile range (IQR) and range. Percentages were calculated on the number of patients with available information, and the denominator is given for each result. Given the extent and the differential pattern of missing data, and the absence of information on confounders, no statistical test was performed and no inferential comparison between groups was attempted. A sensitivity analysis restricted to patients treated with breast-conserving surgery was also performed. Analyses were performed with Python.

3. RESULTS

3.1 Population and use of techniques

During the study period, 572 patients had a recorded boost technique and were analysed (Figure 1). The boost was sequential in 501 patients (87.6%) and simultaneous integrated in 71 (12.4%). Patient characteristics are shown in Table 2. All 71 SIB treatments were delivered in 2021, whereas 362 of the 491 sequential treatments with a known year (73.7%) were delivered in 2022 (2020: 2; 2021: 105; 2023: 22; year missing: 10). Year of treatment was taken from the radiotherapy start date or, when missing, the simulation date; treatment dates in the analysed cohort ranged from 2020 to 2023. The two techniques were therefore used in largely different periods, and no trend in uptake over time can be described.

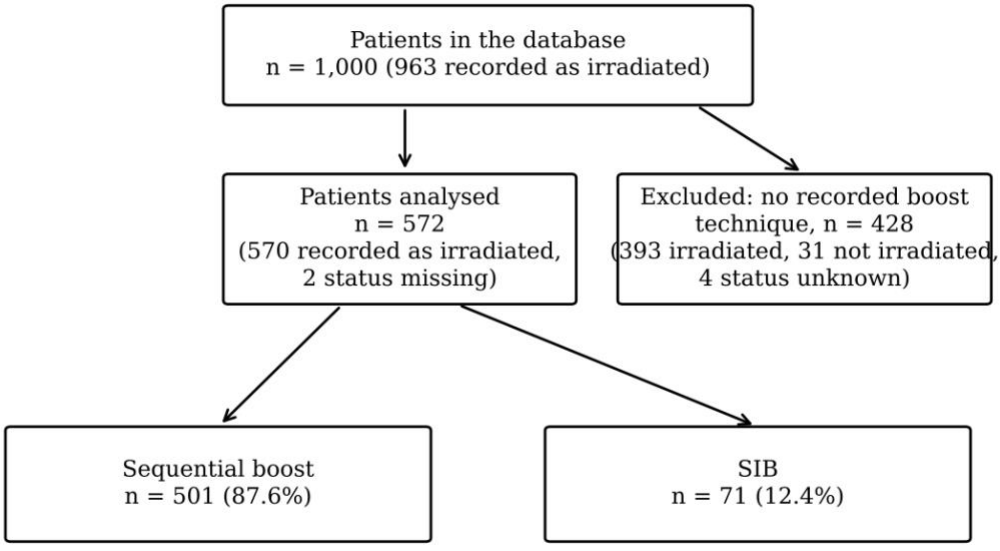


Figure 1. Flow chart of patient selection. Of 1,000 patients in the database (963 recorded as irradiated), 428 had no recorded boost technique and were excluded (393 irradiated, 31 not

irradiated, 4 with radiotherapy status missing or not specified) → 572 patients analysed (570 recorded as irradiated, 2 status missing) → sequential boost (n = 501) / SIB (n = 71).

Table 2. Patient characteristics by boost technique.

Characteristic	Sequential boost (n = 501)	SIB (n = 71)
Age, years, median (IQR)	51 (42–58)	52 (45–60)
Type of surgery: breast-conserving / mastectomy, n (%)	230 (46.0%) / 268 (53.6%)	21 (30.0%) / 48 (68.6%)
pT stage, n (%)	pT0/is 70 (14.5%); pT1 100 (20.7%); pT2 238 (49.2%); pT3 59 (12.2%); pT4 11 (2.3%); pTx 6 (1.2%)	pT0/is 2 (2.9%); pT1 17 (25.0%); pT2 33 (48.5%); pT3 12 (17.6%); pT4 4 (5.9%)
pN stage, n (%)	pN0 231 (47.7%); pN1 145 (30.0%); pN2 77 (15.9%); pN3 26 (5.4%); pNx 5 (1.0%)	pN0 21 (30.9%); pN1 19 (27.9%); pN2 22 (32.4%); pN3 6 (8.8%)
Endocrine therapy, n (%)	388 (77.9%)	55 (77.5%)
Regional nodal irradiation, n (%)	353 (71.6%)	57 (80.3%)
Planning technique: 3D-CRT / IMRT / VMAT, n (%)	500 (100%) / 0 / 0	71 (100%) / 0 / 0
Year of treatment, n (%)	2020: 2 (0.4%); 2021: 105 (21.4%); 2022: 362 (73.7%); 2023: 22 (4.5%)	2021: 71 (100%)

Percentages are calculated on patients with available information. Missing values (sequential / SIB): age 1 / 2; type of surgery 1 / 1 (mixed surgery 2 / 1, not shown); pT 17 / 3; pN 17 / 3; endocrine therapy 3 / 0; regional nodal irradiation 8 / 0; planning technique 1 / 0; year of treatment 10 / 0; body mass index not recorded. pT0/is includes ypT0.

3.2 Completeness and consistency of recorded data

The completeness of the main variables is shown in Table 3. Reported acute toxicity was available for almost all patients in both groups, whereas radiodermatitis grade was recorded for only 16.0% of patients in the sequential group and for a single patient in the SIB group. Overall treatment time showed a differential pattern of missing data: it was available for 9.8% of patients in the sequential group but for 81.7% in the SIB group. The recorded median boost dose was 11.2 Gy in both groups; this value is consistent with the sequential schedule (4 × 2.8 Gy) but not with the SIB schedule (48 Gy in 15 fractions). Moreover, 70 of the 71 SIB-labelled patients had a recorded whole-breast dose of 42 Gy in 2.8 Gy fractions, i.e. that of the sequential schedule, a boost of 11.2 Gy was recorded for only 19 of them, and a boost dose of 48 Gy was recorded for none. Where the information was recorded, no treatment interruption was noted in either group (448 and 67 patients, respectively).

Table 3. Completeness of the main variables by boost technique.

Variable	Sequential boost (n = 501)	SIB (n = 71)
Reported acute toxicity	489 (97.6%)	69 (97.2%)
Radiodermatitis grade (CTCAE)	80 (16.0%)	1 (1.4%)
Overall treatment time	49 (9.8%)	58 (81.7%)
Treatment interruption	448 (89.4%)	67 (94.4%)
Boost dose consistent with protocol	Yes (median 11.2 Gy)	No (median 11.2 Gy recorded vs 48 Gy expected)

Values are numbers (%) of patients with a non-missing value. CTCAE, Common Terminology Criteria for Adverse Events; SIB, simultaneous integrated boost.

3.3 Acute toxicity

Acute toxicity was reported in 66 of 489 patients with available information in the sequential group (13.5%) and in 1 of 69 in the SIB group (1.4%) (Table 4). Among the 80 patients of the sequential group with a recorded radiodermatitis grade, 12 (15%) had grade ≥ 2. In the SIB group, a single patient had a recorded grade, which does not allow estimation of the frequency of grade ≥ 2 radiodermatitis.

Table 4. Acute toxicity by boost technique.

Technique	N	Reported acute toxicity	Radiodermatitis grade ≥ 2 (CTCAE)
Sequential boost	501	66/489 (13.5%)	12/80 (15%)
SIB	71	1/69 (1.4%)	1/1 (not interpretable)

Percentages are calculated on patients with available information. CTCAE, Common Terminology Criteria for Adverse Events; SIB, simultaneous integrated boost.

3.4 Overall treatment time

Overall treatment time was available for 49 patients in the sequential group and 58 in the SIB group (Table 5). The median was 21 days (IQR 20–24) in both groups. In the SIB group, this value is consistent with the minimum expected duration of 19 days. In the sequential group, it is shorter than the minimum expected duration of 25 days, indicating that the recorded end date frequently did not correspond to the last boost session. In the SIB group, a minimum value of 5 days is incompatible with a complete course and suggests a data-entry error, an incomplete record or a treatment stopped prematurely; in the sequential group, the minimum was 17 days, also below the 25 days expected. Four free-text entries in the sequential group ("5 days/7"), which describe the weekly schedule rather than a duration, were not counted as evaluable.

Table 5. Recorded overall treatment time by boost technique.

Technique	N evaluable	Minimum expected (days)	Median (days)	IQR	Min–Max
Sequential boost	49	25	21	20–24	17–32
SIB	58	19	21	20–24	5–29

Overall treatment time: calendar days from first to last session, both included. Minimum expected values assume five fractions per week without interruption. IQR, interquartile range; SIB, simultaneous integrated boost.

3.5 Sensitivity analysis restricted to breast-conserving surgery

Because a boost is meaningful mainly after breast-conserving surgery, the analyses were repeated in the 251 patients treated with this approach (230 sequential, 21 SIB-labelled). The doses recorded for SIB-labelled patients remained those of the sequential schedule: 42 Gy to the breast in 20 of 21 and a boost of 11.2 Gy in 18 of 21. Reported acute toxicity was available for 228 sequential and 20 SIB patients and was reported in 34 (14.9%) and 1 (5.0%),

respectively. Radiodermatitis grade was recorded for 35 sequential patients (15.2%; grade 1 in 28 and grade 2 in 7) and for 1 SIB patient (grade 2). Overall treatment time was evaluable for 29 sequential patients (12.6%; median 22 days, IQR 20–24, range 19–28) and 18 SIB patients (85.7%; median 24 days, IQR 21–25, range 5–28). All SIB-labelled patients were treated in 2021 and most sequential patients in 2022 (152 of 223 with a known year). These results do not change the conclusions: completeness remained low for radiodermatitis grade and, in the sequential group, for overall treatment time, and the SIB label was not supported by the recorded doses.

4. DISCUSSION

In this single-centre cohort of 572 patients, sequential boost remained by far the dominant technique (almost 88% of cases), SIB being used only marginally. The main finding is that routinely recorded data were insufficient to compare the two techniques: radiodermatitis grade was almost never recorded, overall treatment time was missing for most sequential patients, with a differential pattern between groups, and some recorded values were inconsistent with the institutional protocol. To our knowledge, few studies have documented these gaps explicitly, although they directly condition the use of real-world data to evaluate radiotherapy techniques.

4.1 Acute toxicity

Reported acute toxicity appeared markedly lower in the SIB group (1.4% versus 13.5%), but this should not be read as an advantage of SIB. First, radiodermatitis was almost undocumented in this group, with a single graded observation. Second, “reported toxicity” rests on non-standardised recording; a rate of 13.5% in the sequential group is itself far below the frequency of grade 1 radiodermatitis expected after breast irradiation, which points to under-reporting in both groups, possibly more marked for SIB, a technique used in a single year in this cohort, whose skin surveillance may have been less systematically recorded. Third, the two groups are not comparable a priori: the choice of technique was not randomised, and SIB may have been reserved for particular patient profiles, breast volumes or treatment periods.

The two schedules also differ in biological intensity (Table 1). The sequential schedule delivered a higher EQD2 to the whole breast (44.8 versus 42.3 Gy for acute effects, $\alpha/\beta = 10$ Gy) and to the tumour bed (56.7 versus 52.8 Gy), despite a lower dose per fraction in the boost volume (2.8 versus 3.2 Gy). Any difference in skin toxicity between groups would therefore reflect, at least in part, a difference in dose intensity rather than the boost technique itself. With

α/β = 3.5 Gy, the tumour-bed EQD2 was also higher with the sequential schedule (60.9 versus 58.5 Gy), which should be kept in mind if local control is analysed in the future. These calculations assume that patients were treated according to the protocol, which the doses recorded in the database do not confirm.

Published data on the acute tolerance of SIB are reassuring overall but not uniform. IMPORT HIGH reported a 5-year ipsilateral breast tumour relapse incidence below 5% in all arms, and low rates of moderate or marked adverse events with small boost volumes [7]. The NRG/RTOG 1005 report described grade ≥ 3 adverse events in 3.5% of patients with hypofractionated whole-breast irradiation and a concurrent boost versus 3.3% with conventional treatment and a sequential boost [9]. By contrast, in an analysis of acute toxicity in the IMRT-MC2 trial, in which SIB was delivered with normofractionated intensity-modulated radiotherapy, any-grade radiodermatitis did not differ significantly at the end of treatment, but grade 2 and grade 3 radiodermatitis were significantly more frequent in the SIB arm (29.1% versus 20.1% and 3.5% versus 2.3%, respectively), whereas breast pain at first follow-up was more frequent after sequential boost [13]. Skin toxicity with SIB therefore appears to depend on the fractionation scheme, the planning technique and the boost volume, none of which could be fully explored in our dataset. In the sequential group, 15% of the patients with a documented grade had grade ≥ 2 radiodermatitis, but this proportion cannot be extrapolated to the whole group: grade was probably recorded mainly when toxicity was notable, which would overestimate the true proportion.

4.2 Overall treatment time

The main argument in favour of SIB is a shorter treatment. With the schedules used here, the SIB course comprises 15 fractions and the sequential course 19, so the expected saving is four sessions, or about one working week (minimum 19 versus 25 days). This saving is smaller than in IMPORT HIGH (3 weeks versus about 4.5 weeks), where the sequential boost comprised eight fractions [7]. We observed the same median overall treatment time of 21 days in both groups. This value is consistent with the SIB schedule but shorter than the minimum expected for the full sequential course, which suggests that the recorded end date in the sequential group often corresponded to the end of whole-breast irradiation rather than of the boost. Combined with the very low completeness of this variable in the sequential group and the implausible minimum values, the absence of difference in duration must be interpreted as a limitation of data quality, not as an absence of benefit of SIB.

4.3 Strengths and limitations

The strengths of this work are its sample size, the inclusion of all patients with a recorded boost technique in a reference centre over four years, the explicit reporting of denominators and completeness for each variable, and the comparison of recorded values with protocol-expected values. Its limitations are substantial: the retrospective, single-centre design; the imbalance between groups (501 versus 71 patients); the large and differential amount of missing data; the non-standardised recording of reported toxicity; the use of institutional protocol schedules rather than patient-level fractionation data; the probable misclassification of the boost technique, since the doses recorded for SIB-labelled patients (42 Gy to the breast, boost of 11.2 Gy) correspond to the sequential schedule, which also weakens the EQD2 comparison based on protocol schedules; the use of three-dimensional conformal planning in all SIB patients, whereas SIB is usually delivered with intensity modulation; the inclusion of patients treated after mastectomy (55% of the cohort), in most of whom no boost was recorded; the absence of adjustment for factors that may influence skin toxicity (breast volume, body mass index, systemic treatments, planning technique, nodal irradiation); and the lack of data on local control and cosmetic outcome. The toxicity and duration results must therefore be considered exploratory.

4.4 Implications for practice

These findings support the implementation of a minimum dataset for breast radiotherapy, recorded prospectively for every patient whatever the technique: (i) delivered fractionation and boost technique, verified against the treatment planning system; (ii) dates of the first and last sessions, including the boost, and any interruption with its reason; (iii) weekly CTCAE grading of radiodermatitis during treatment and at the end of treatment; (iv) planning technique and boost volume; and (v) late toxicity, cosmetic outcome and local control during follow-up. A targeted audit of the overall treatment time variable, followed by a prospective cohort with adjusted or matched comparison, is the next step before any conclusion on the relative merits of the two techniques in our setting.

5. CONCLUSION

In this single-centre cohort, sequential boost largely dominated practice, while SIB remained rarely used. Routinely recorded data did not allow a valid comparison of acute skin toxicity or overall treatment time between the two techniques, mainly because of missing radiodermatitis grades, incomplete treatment dates and inconsistent coding. Structured prospective recording, based on a minimum dataset, is a prerequisite for evaluating SIB in our setting.

ACKNOWLEDGEMENTS

The authors have no acknowledgements to declare and report no conflicts of interest.

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