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Safety outcomes of bone conduction and middle ear implants: a systematic review

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FOREWORD

Since its first publication in 2016, the "Safety White Paper" has gained much attention from internal and external stakeholders. Many professionals from different areas of expertise have commented on it. Consequently, the 5th revision of this document is released with several updates that express MED-EL's commitment to meeting highest quality standards in clinical research. Major changes include the following:

1) Inclusion criteria have been changed with regards to publication date. Articles published between 01. Jan 2012 and 31. Dec 2018 are now included.

2) Surgical actions performed to treat adverse events, and becoming a non-user, are now separately reported as sequelae to an adverse event and not as an adverse event per se.

3) Incidence rate (cases in 100 patients and 6 months) is now reported as primary outcome unit to enhance comparability of results among devices.

4) Special emphasis is put on the timing of adverse events, resulting in detailed safety profiles for each device over time.

1. INTRODUCTION

Safety assessment and clinical risk management are the fundamental principles of value-based healthcare. Therefore, medical devices are exposed to ongoing scrutiny (directly or indirectly) by patients, health care professionals and authorities worldwide. In order to take informed decisions, these stakeholders need to balance risks and benefits associated with a specific device and thus require evidence in terms of clinical outcomes and safety. However, comprehensively assessing safety profiles of medical devices is quite difficult. While common adverse events (AEs) are usually captured during pre-market studies, large patient populations are needed to explore less common AEs. Post-market follow-up trials are performed to this end, but rarely include more than 100 patients. Incidence rates of AEs estimated from such small populations are expected to vary considerably[1]. Systematically reviewing results published by others can help to increase the reliability of estimates. As an example, Shapiro and colleagues[2] investigated the safety of bone-anchored hearing aids in children by means of meta-analysis. While they were the first to do so, this approach has one crucial weakness: Meta-analysis can estimate an average effect among studies included, but it does not increase the sample size needed to raise accuracy of incidence rates estimated in single studies (i.e., the average of unreliable outcomes is still unreliable). Similarly, Schwab and colleagues[3] recently published a comprehensive review on safety in BCIs and MEIs using descriptive statistics to summarize device-specific rates of AEs found by individual studies.

An alternative approach is to pool patients from single studies into one big patient population, where each single study contributes to overall 'person-time' according to sample size and mean follow-up (F/U). Incidence rates estimated in this way might be much more realistic compared to rates estimated at study-level (i.e., via meta-analysis or descriptive statistics). Even though sample size can be increased by pooling data from different studies, finding a meaningful cut-off for sample size is anything but easy. The following rationale might be applied as a pragmatic rule: In order to detect AE rates as low as 1 event in 100 patients, at least 100 patients should have been followed up per time-unit. Clearly, the precision of any estimate will increase with larger sample size.

This white paper reports incidence rates of sequelae, major AEs and minor AEs based on pooled patient data from a systematic review of literature reporting on safety outcomes with bone conduction implants (BCIs) and middle ear implants (MEIs). The document gives a brief overview of the devices currently available[4], including hearing loss indications and performance characteristics (see Figure 1). In the results section, incidence rates based on the pooled population approach are summarized separately for each device. Two separate outcomes are reported: 1) A „6-month Average" incidence rate, which is calculated from events reported over a mean F/U time. 2) Incidence rates for consecutive 6-month intervals, which are calculated from events reported at specific times during F/U. While average 6-month rates are based on a bigger sample size, they can be biased if events do not occur at a constant rate over time. In contrast, separate rates for consecutive F/U intervals are based on smaller sample sizes, but are able to capture different event rates over time, and are therefore better comparable among devices. Both estimates convey valuable information and should not be evaluated independently. In general, 6-month categories have been chosen because they reflect common timeframes in clinical trials and provide enough resolution for a detailed safety profile. Following on the rationale mentioned earlier, estimates based on less than 100 samples will be considered unreliable. Summaries also include lists of most frequent sequelae/AEs and their incidence rates within the first year post-surgery. A full list of sequelae/AEs and corresponding incidence rates can be found in the Appendix. Finally, a comparative summary is provided, based on cumulative incidence rates from the first 12 months post-surgery.

Unfortunately, safety outcomes are rarely reported at

patient level, that would allow for stratified analyses by indication or other confounders. Whenever studies reported exclusively on safety in children for any device, summaries include a special section on safety in children.

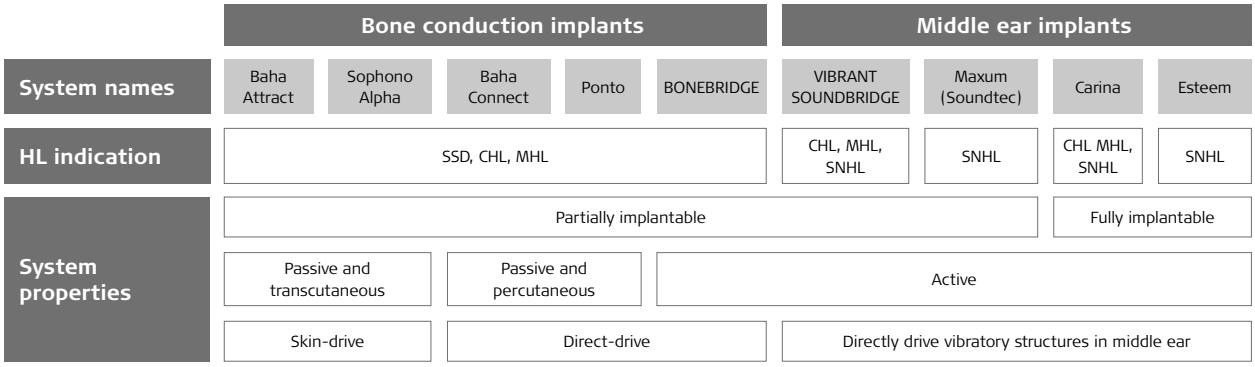

Figure 1: Schematic overview of included devices with corresponding hearing loss indications and main system properties (modified from Reinfeldt et al. 2015).

1.1. Bone Conduction Implants

Depending on their design, three types of BCIs can be distinguished:

Active BCIs (MED-EL's BONEBRIDGE)
The active component is located within the implantable part of the system. In active devices, the advantage of direct stimulation of the skull bone is combined with the advantage of intact skin. The light-weight audio processor is held in place by magnetic force.

Passive and transcutaneous BCIs (Medtronic's Sophono Alpha, Cochlear's Baha Attract)
In transcutaneous bone-anchored systems, a titanium fixture is surgically embedded into the skull bone, but instead of an abutment, a magnetic plate is screwed into the fixture and the wound is closed. After healing is completed, a sound processor is held over the implant by magnetic force. Because the actuator drives the skin, signal attenuation needs to be compensated by increased output force and/or increased magnetic force to press the audio-processor onto the skin. The fixture needs to achieve osseointegration for the system to work efficiently.

Passive and percutaneous BCIs (Cochlear's Baha Connect series, Oticon Medical's Ponto)
These devices are traditionally referred to as 'BAHAs' (bone-anchored hearing aids). A titanium fixture is surgically embedded into the skull bone with an abutment penetrating the skin. A sound processor that generates is clipped onto this abutment and the skull bone is stimulated by the actuator via the titanium fixture. Vibrations are transmitted to the cochlea for further natural sound processing. The fixture needs to achieve osseointegration for the system to work efficiently.

1.2. Middle Ear Implants

Partially implantable middle ear implants (MED-EL's VIBRANT SOUNDBRIDGE, Ototronix's Maxum)
Partially implantable middle ear implants consist of an audio processor (including the microphone) and an implant component. An actuator that is coupled to the ossicular chain transduces signals to the inner ear for further natural sound processing. Depending on the system, the audio processor is located over the implant (SOUNDBRIDGE) or in the ear canal (Maxum).

Fully implantable middle ear implants (Envoy Medical's Esteem, Cochlear's Carina)
The Carina and Esteem fully implantable MEIs differ substantially by design. In the former, microphone and audio processor are both implanted under the skin. The battery is charged by a coil placed on the skin over the implant. The design of the Esteem includes no microphone at all, because sound is received by a sensor coupled to the incus. The incudostapedial joint is permanently disrupted and replaced by the implant, which receives, processes and transduces signals to an actuator for further stimulation of the inner ear. The battery is not rechargeable and needs to be replaced with a surgical procedure.

2. METHODS

Literature search

The aim of this systematic review was to identify all articles that reported on safety outcomes associated with bone conduction implants published between 01. Jan 2012 and 31. Dec 2018 and all articles that reported on safety outcomes associated with middle ear implants published between 01. Jan 1996 and 31. Dec 2018. This was accomplished by a two-step procedure: First, repeating the full-text screening process from revision 4 of this document using more stringent exclusion criteria and filtering out articles on BCIs published before 01. Jan 2012, and second, performing a new search to find articles on BCIs and MEIs published between 01. Jan 2017 and 31. Dec 2018. In the following, each step is described in detail:

1) Revision 4 of this document included 811 articles in the full-text screening process. Applying more stringent exclusion criteria resulted in exclusion of 661 articles due to the following reasons: not original article (N = 182), not reporting on adverse events (N = 182), not including human patients or less than five patients (N = 95), not hearing implant related (N = 64), patient population overlap (i.e., outcomes from same patient population reported in more than one article; N = 28), inconclusive reporting (i.e., ambiguous reporting of outcome parameters or demographics; N = 19), being a study on explants only (N = 1), being a duplicate (N = 1) and being a study on an investigational device (N = 1). Eighty-six (N=86) were articles on BCIs published before 01 Jan 2012, resulting in 150 articles for further analysis.

2) In order to find articles published between 01. Jan 2017 and 31. Dec 2018 a new search was performed using streamlined search terms (Appendix 1). Two-hundred and sixty-eight (N=268) articles were found. Eleven (N = 11) additional articles were known to the authors. Of these 279 articles, 231 were excluded for the following reasons: not hearing implant related (N = 140), not original article (N = 29), not including human patients or less than five patients (N = 17), not reporting on adverse events (N = 17), not English or German (N = 8), specialized topic w/o outcome (N = 7), inconclusive reporting (N = 5), patient overlap (N = 4), published before 01. Jan 2017 (N = 2), investigational device (N = 1), selective population (N=1). The remaining 48 articles were included for further analysis.

150 articles from revision 4 were combined with 48 articles from the new search, resulting in a full set of 198 articles reporting on safety outcomes with bone conduction and middle ear implants.

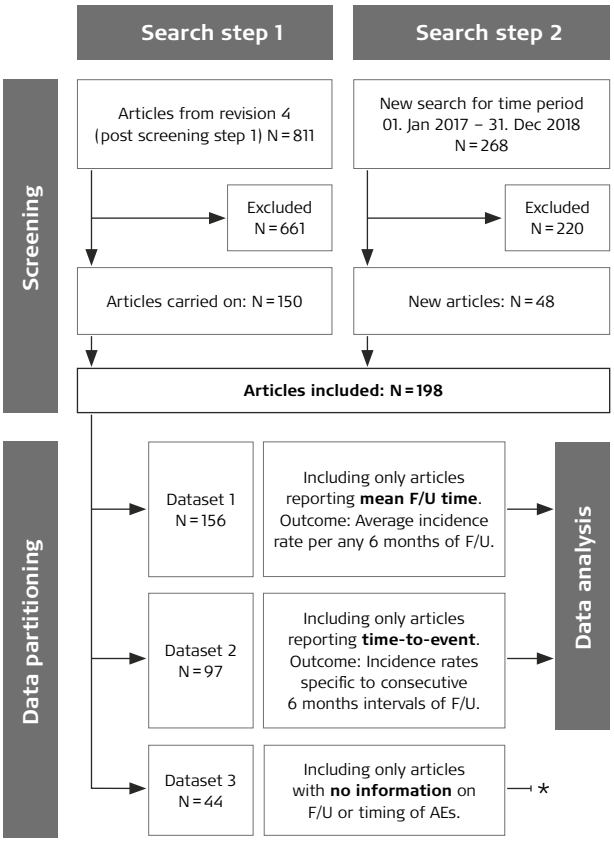

Figure 2: Flow diagram summarizing article screening and data partitioning. Note that some articles were included in more than one partitioned dataset and therefore sample sizes do not sum up to N = 198. *Dataset 3 was not analyzed quantitatively due to missing information, but sequelae and AEs reported in these articles are summarized in Appendix 2.

Data synthesis

From each of the final 198 articles, the following safety outcome parameters were extracted: 1) Number of implants that were followed up, 2) Number of sequelae and adverse events, 3) Type of sequelae and adverse events, 4) Timing of sequelae and adverse events, 5) Mean follow-up (F/U) time.

For each article, person-time was calculated as the product of implant number (sample size) and mean F/U time in months. Average incidence rate per 6 months was calculated as the sum of all events reported divided by person-time and multiplied by six. Incidence rates for consecutive 6-month F/U intervals were calculated by dividing events reported within the respective time interval by the number of implants (sample size) followed up over this interval.

How to read outcome figures

In the results section, you will find one page per device summarizing the information gathered from both datasets 1 and 2 (as shown in Figure 3). Dataset 3 was not analyzed quantitatively due to missing time information, but sequelae and AEs reported in these articles are qualitatively summarized in Appendix 2. Figures 4-12 provide an overview of results from both analyzed datasets. Briefly, each figure consists of two panels, summarizing the number of patients (A) and the incidence rates calculated from pooled data (B). Both panels are vertically split in two sections, each one summarizing data from dataset 1 (A1 and B1) and dataset 2 (A2 and B2), respectively. The specific information provided by each of these 4 sections is illustrated in Figure 3.

The red line in panel A indicates the threshold of 100 pooled patients. Incidence rates calculated from less than 100 patients may be considered unreliable or biased due to low sample size. The number of F/U time intervals displayed in sections A2 and B2 varies with the availability of data points for each device. By default five intervals (0–30 months) are displayed. In case of less F/U time coverage, intervals with missing data are indicated by NA.

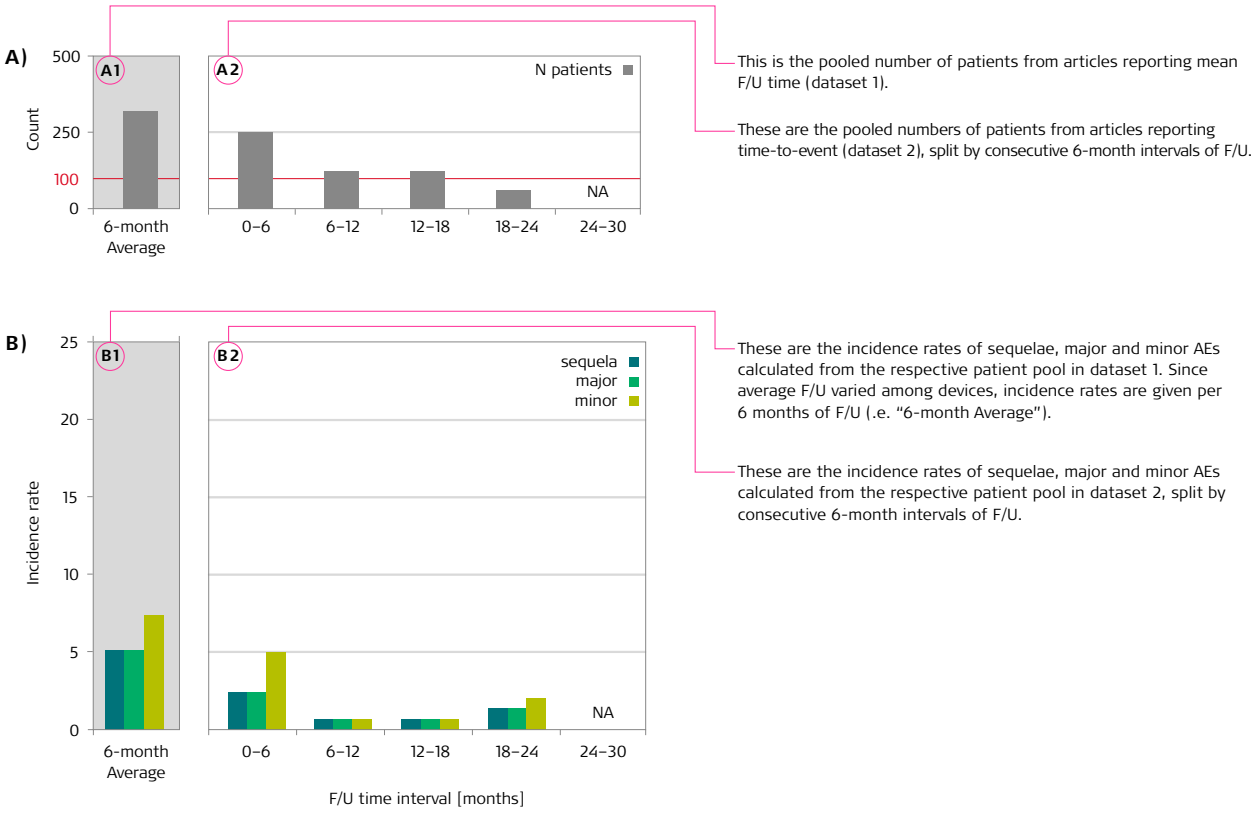

Figure 3: Example of main outcomes figure summarizing patient numbers and incidence rates for any specific device, including explanations for sections A1 through B2.

3. BONE CONDUCTION IMPLANTS

3.1. BONEBRIDGE (MED-EL)

Pooled patient population

Twenty-seven articles reported on safety outcomes after BONEBRIDGE implantation in 463 patients. Seven articles[5-11] did not report any time horizon for AEs or patient follow-up and were therefore excluded from further analyses. In the remaining 20 articles[12-31] 27 adverse events (in 27 patients) and 6 sequelae (in 6 patients) were reported in a total population of 347 patients (Figure 4 – A1) over an average F/U time of 10.9 months. Fourteen articles[13-21, 23, 25, 27, 30, 31] reported time-to-event for 19 AEs and 4 sequelae in a population of 271 patients over F/U times of up to 30 months (Figure 4 – A2).

Frequency of adverse events

The average incidence rates of sequelae, major and minor AEs were 0.96, 0.8 and 3.5 cases in 100 patients and 6 months, respectively (Figure 4 – B1). Patients experiencing events had on average 1.0 AE or 1.0 sequelae over their F/U period.

Minor AEs mainly occurred within the first 6 months after surgery (i.e., 5.17 cases in 100 patients; Figure 4 – B2), while major AEs and sequelae occurred less than once in 100 patients (each 0.74 cases in 100 patients). Both, sequelae and AEs dropped to 0.56 cases in 100 patients after 6 months and no further AEs were noted up to 24 months post-surgery. The apparent increase of major AEs and sequelae at the 24–30 months interval (both 1.64) could be explained by low patient number (N=61) in this F/U interval and in fact corresponded to only one patient with sudden loss of benefit and subsequent re-implantation. No device defect was found upon examination of the explanted device in this case[21].

Both, 6-month average and consecutive incidence rates were lower than 1 case in 100 patients for major AEs and sequelae. This may be a combined consequence of the light-weight audio-processor and the active implant. In general, if adverse events occurred, they were associated with the implantation procedure rather than with usage of the device.

Types of adverse events

Overall, 15 types of adverse events and 3 types of sequelae were reported in the reviewed literature. The complete list of sequelae and AEs is given in Appendix 3. Table 1 lists sequelae and adverse events that were recorded at frequencies above 1 case in 100 patients within the first year after surgery.

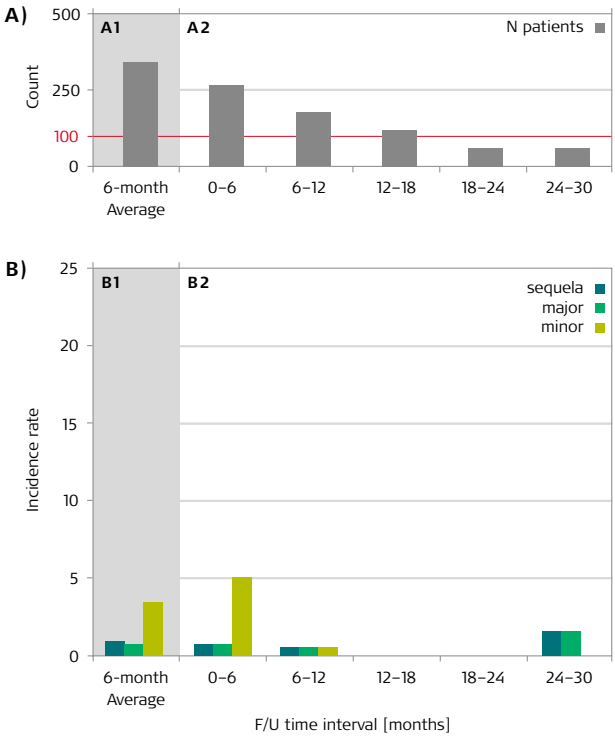

Figure 4: Incidence rates (cases in 100 patients and 6 months) of adverse events and sequelae after BONEBRIDGE surgery. A) Pooled number of patients followed-up across studies reporting mean F/U time (A1) and across studies reporting time-to-event (A2). B) Average incidence rate calculated from 20 articles reporting mean F/U time (B1) and incidence rates for consecutive 6-month intervals calculated from 14 studies reporting time-to-event (B2).

Table 1: Adverse events and sequelae observed at incidence rates above 1 case in 100 patients within one year after BONEBRIDGE surgery. (Inc. rate = 12-month incidence rate)

	Event name	Type	Inc. rate
1	Skin irritation (erythema) or itching	minor	2.40
2	Wound infection	minor	1.85

Safety in children vs. adults

Five articles [12, 14, 16, 20, 26] including 61 patients specifically reported on safety with the BONEBRIDGE in children. No sequelae or major AEs were reported. Mean F/U time was 9.28 months and the average 6-month incidence rate of minor AEs was 7.42 cases in 100 patients. This is slightly higher compared to the adult and mixed population (2.14 cases), but all minor AEs occurred within the first 6 months post-surgery and no further AEs occurred up to 18 months of F/U.

3.2. Baha Attract (Cochlear Ltd.)

Pooled patient population

Fifteen articles reported on safety outcomes after Baha Attract surgery in 489 patients. Two articles[32-46] did not report any time horizon for AE occurrence or patient follow-up and were therefore excluded from further analyses. In the remaining 13 articles[34-46], 196 adverse events (in 119 patients) and 10 sequelae (in 9 patients) were reported in a total population of 466 patients (Figure 5 – A1) over an average F/U time of 6.09 months. Eleven articles[34-37, 40-46] reported time-to-event for 158 AEs and 10 sequelae in 331 patients (Figure 5 – A2) over F/U times up to 12 months.

Frequency of adverse events

The average incidence rates of sequelae, major and minor AEs were 2.12, 0.63 and 41.04 cases in 100 patients per 6 months, respectively (Figure 5 – B1). Patients experiencing events had on average 1.56 AEs or 1.1 sequelae over their F/U period.

Minor AEs were predominant in the first and second F/U interval after surgery with 42.3 and 12.5 cases in 100 patients, respectively (Figure 5 – B2). Major AEs and sequelae were seen within the first 6 months at rates of 0.91 and 3.02 cases in 100 patients, respectively. No long-term F/U data (>12 months) is currently published for this device.

Both, 6-month average and F/U-specific incidence rates were elevated for minor AEs. Although the rate dropped to 12.5 cases in 100 patients between 6 and 12 months, the absence of published long-term data precludes any further conclusion. Since some of the reported minor AEs were associated with device use rather than with the surgical intervention, it will be interesting to see whether minor AEs will level out in the long run.

Types of adverse events

Overall, 14 types of adverse events and 3 types of sequelae were reported in the reviewed literature. The complete list of AEs is given in Appendix 3. Table 2 lists sequelae and adverse events that were recorded at frequencies above 1 case in 100 patients within the first year after surgery.

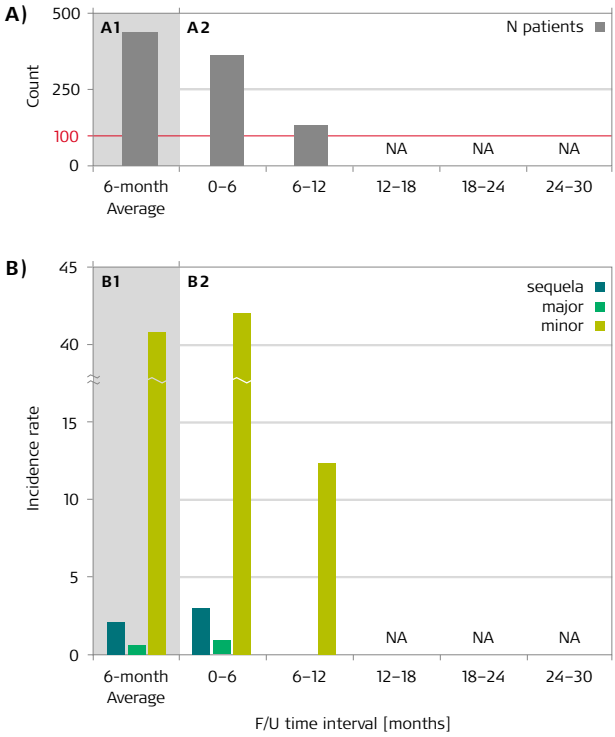

Figure 5: Incidence rates (cases in 100 patients per 6 months) of adverse events and sequelae after Baha Attract surgery. A) Pooled number of patients followed-up across studies reporting mean F/U time (A1) and across studies reporting time-to-event (A2). B) Average incidence rates calculated from 13 articles reporting mean F/U time (B1) and incidence rates for consecutive 6-month intervals, calculated from 11 articles reporting time-to-event (B2). (N/A = no data available)

Table 2: Adverse events and sequelae observed at incidence rates above 1 case in 100 patients within one year after Baha Attract surgery. (Inc. rate = 12-month incidence rate)

	Event name	Type	Inc. rate
1	Numbness around the implant	minor	22.22
2	Postoperative pain	minor	11.48
3	Paresthesia/Dysesthesia (abnormal sensation) of the skin	minor	7.42
4	Problems finding correct magnet strenght to prevent slippage (too weak) or skin irritation (too strong)	minor	4.69
5	Pain around the implant site, due to device use	minor	3.63
6	Skin edema or erythema	minor	2.34
7	Skin tenderness or redness	minor	1.21
8	Explantations (medical reason, no benefit, patient's request)	sequela	1.21

Safety in children vs. adults

Two articles[34, 39] specifically reported on safety in 16 children over a mean F/U time of 4.69 months. No sequelae or major AEs were reported, but two children experienced minor AEs. Technically, this corresponded to an average incidence rate of 24.0 cases in 100 implants and 6 months, but confidence in this rate estimate is limited due to low sample size. However, this was considerably lower compared to the adult and mixed population, where the average incidence rate of minor AEs was 102.79 cases.

3.3. Sophono Alpha (Medtronic)

Pooled patient population

Fifteen articles reported on safety outcomes after Sophono Alpha surgery in 172 patients. Three articles[47-49] did not report any time horizon for AE occurrence or patient follow-up and were therefore excluded from further analyses. The remaining 12 articles[34, 39, 45, 50-58] reported on 63 adverse events (in 47 patients) and 27 sequelae in (26 patients) in a total population of 137 patients (Figure 6 – A1) over an average F/U time of 14.69 months. Eight articles[34, 45, 50-52, 54-56] reported on the timing of adverse events in 76 patients (Figure 6 – A2) over F/U times up to 36 months.

Frequency of adverse events

The average incidence rates of sequelae, major and minor AEs were 8.05, 1.79 and 16.99 cases in 100 patients and 6 months, respectively (Figure 6 – B1). Patients experiencing events had on average 1.34 AEs or 1.04 sequelae over their F/U period.

The incidence rate of sequelae was highest within the first 6 months post-surgery (21.05 cases), but high rates were seen at 12-18 months (14.29 cases) and at 30-36 months (16.67 cases) as well (Figure 6 – B2). Major AEs increased up to 5.08 cases between 6 and 12 months but were absent afterwards. Minor AEs occurred at a very high rate (60.53 cases), but only within the first 6 months post-surgery.

The evidence on safety with the Sophono Alpha device is far from clear. A moderate number of studies with low sample size reported different AE rates ranging from very low to very high. Estimates for specific F/U-intervals suffered from low or very low sample sizes and were heavily biased towards sequelae. More studies will be needed to increase sample size for more reliable estimates of AE rates following Sophono Alpha surgery.

Types of adverse events

Overall, 21 types of AEs and 6 types of sequelae were reported in the reviewed literature. The complete list of AEs is given in Appendix 3. Table 3 lists sequelae and AEs that were recorded at frequencies above 1 case in 100 patients within the first year after Sophono Alpha surgery.

Safety in children vs. adults

Eight studies [34, 39, 45, 50, 51, 54-56] exclusively examined outcomes in children over a mean F/U of 13.92 months. Average incidence rates of sequelae, major and minor AEs (9.41, 1.76 and 22.34 cases) were lower in children compared to the adult population (17.56, 4.79 and 27.13 cases, respectively).

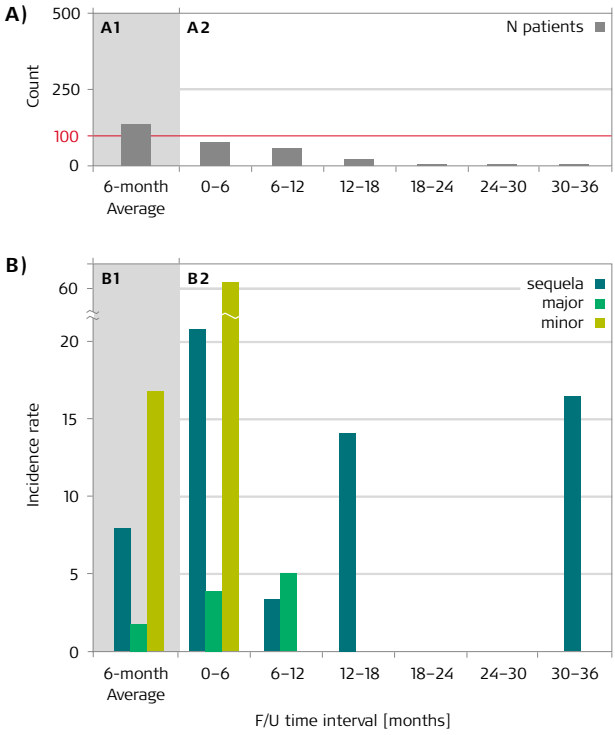

Figure 6: Incidence rates (cases in 100 patients and 6 months) of adverse events and sequelae after Sophono Alpha surgery. A) Pooled number of patients followed-up across studies reporting mean F/U time (A1) and across studies reporting time-to-event (A2). B) Average incidence rates calculated from 12 articles reporting mean F/U time (B1), and incidence rates for consecutive 6-month intervals calculated from 8 articles reporting time-to-event (B2).

Table 3: Adverse events and sequelae observed at incidence rates above 1 case in 100 patients within one year after Sophono Alpha surgery. (Inc. rate = 12-month incidence rate)

	Event name	Type	Inc. rate
1	Pain at AP site	minor	14.47
2	Pressure discomfort	minor	12.98
3	Limited benefit or pausing needed	sequela	11.84
4	Skin edema or erythema	minor	9.21
5	Device falling off the head	minor	7.89
6	Stopped using device	sequela	7.34
7	Skin ulceration	minor	2.63
8	Inflammation	minor	2.63
9	Infection	minor	2.63
10	Hematoma ear	minor	2.63
11	Tingling of the skin	minor	2.63
12	Implant/device failure	major	2.63
13	Explantation	sequela	2.63
14	Local abscess	minor	1.32
15	Headaches	minor	1.32
16	Skin breakdown	minor	1.32
17	Reimplantation	sequela	1.32
18	Revision surgery	sequela	1.32

3.4. Ponto (Oticon Medical)

Pooled patient population

Twelve articles reported on safety outcomes after Ponto surgery in 386 patients. Two articles[59, 60] did not report any time horizon for AE occurrence or patient follow-up and were therefore excluded from further analyses. The remaining 10 articles[61-70] reported on 197 AEs (in 119 patients) and 15 sequelae (in 15 patients) in a total population of 334 patients (Figure 7 – A1) over an average F/U time of 10.27 months. All 10 articles reported on time-to-event.

Frequency of adverse events

The average incidence rates of sequelae, major and minor AEs were 2.62, 3.5 and 30.97 cases in 100 patients and 6 months, respectively (Figure 7 – B1). Patients experiencing events had on average 1.66 AEs or 1.0 sequelae over their F/U period.

Major AEs and sequelae were highest within the first six months post-surgery (5.39 and 4.79 cases, respectively), decreased between 6 and 12 months (to 1.46 and 0.98 cases, respectively) and were absent in longer F/U data (Figure 7 – B2). The rate of minor AEs was very high (53.59 cases) within the first 6 months post-surgery, but decreased rapidly to 5.85 cases (6-12 months) and 3.23 cases (18-24 months).

While data from the first 12 months post-surgery were robust in terms of sample size, long-term data were based on a single study with 31 patients and may not provide reliable estimates.

Types of adverse events

Overall, 19 types of adverse events and 3 types of sequelae were reported in the reviewed literature. The complete list of AEs is given in Appendix 3. Table 4 lists sequelae and adverse events that were recorded at frequencies above 1 case in 100 patients within the first year after Ponto surgery.

Safety in children vs. adults

None of the included articles specifically investigated safety in children.

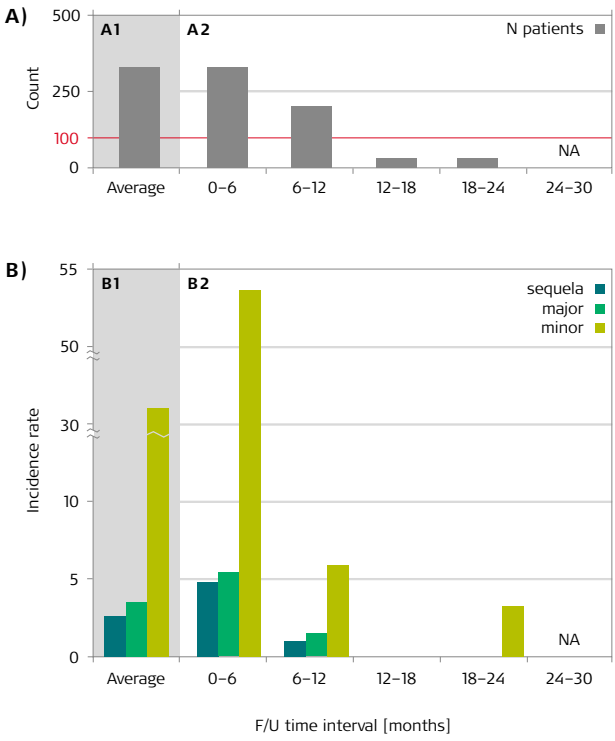

Figure 7: Incidence rates (cases in 100 patients and 6 months) of adverse events and sequelae after Ponto surgery. A) Pooled number of patients followed-up across studies reporting mean F/U time (A1) and across studies reporting time-to-event (A2). B) Average incidence rates (B1) and incidence rates for consecutive 6-month intervals calculated from 10 articles reporting mean F/U time and time-to-event (B2), respectively.

Table 4: Adverse events and sequelae observed at incidence rates above 1 case in 100 patients within one year after Ponto surgery. (Inc. rate = 12-month incidence rate)

	Event name	Type	Inc. rate
1	Holgers grade 1	minor	23.10
2	Holgers grade 2	minor	8.65
3	Inflammation	minor	4.08
4	Abutment exchange	sequela	3.97
5	Holgers grade 3	major	2.88
6	Implant loss/osseointegration failure	major	2.58
7	Wound dehiscence	minor	1.80
8	Revision surgery	sequela	1.20

3.5. Baha Connect (Cochlear Ltd.)

Pooled patient population

Fifty articles reported on safety outcomes after Baha Connect surgery in 2473 patients. Of these, 13 articles[60, 71-82] did not report any time horizon for AE occurrence or patient follow-up and were therefore excluded from further analyses. The remaining 37 articles[40, 42, 55, 57, 83-115] reported on 978 adverse events (in 736 patients) and 401 sequelae (in 290 patients) in a total population of 1889 patients (Figure 8 – A1) over an average F/U time of 31.75 months. Sixteen articles[40, 42, 87, 93-95, 99-101, 103-106, 111, 113, 114] reported on the timing of adverse events in 528 patients (Figure 8 – A2) over F/U times up to 54 months.

Frequency of adverse events

The average incidence rates of sequelae, major and minor AEs were 4.01, 3.68 and 6.1 cases in 100 patients and 6 months, respectively (Figure 8 – B1). Patients experiencing AEs had on average 1.3 AEs or 1.38 sequelae over their F/U period.

Incidence rates of sequelae, major and minor AEs were highest within the first 6 months post-surgery (4.73, 6.82 and 16.86 cases in 100 patients), and levelled out at 1.04, 2.08 and 3.13 between 18 and 24 months post-surgery (Figure 8 – B2). No sequelae or major AEs were reported in the following 3 F/U intervals. However, 42-48 months post-surgery, incidence rates were again at the same level as 24 months post-surgery. This pattern might be explained by true absence of AEs or by the study design used in many long-term studies with the Baha Connect: AEs were mostly registered at fixed F/U intervals (i.e., at 12, 24, 36 or 48 months post-surgery), while ignoring the time in between.

Types of adverse events

Overall, 40 types of adverse events and 7 types of sequelae were reported in the reviewed literature. The complete list of AEs is given in Appendix 3. Table 5 lists sequelae and adverse events that were recorded at frequencies above 1 case in 100 patients within the first year after Baha Connect surgery.

Safety in children vs. adults

Eleven articles[55, 84, 92, 94, 96, 98, 101-104, 107] reported on safety in 426 children over a mean F/U time of 31.88 months. The average incidence rates of sequelae and major AEs were higher in children (10.47 and 8.57 cases in 100 patients per 6 months) compared to the adult population (4.27 and 7.29 cases). Minor AE rates were comparable in children (10.25 cases) and adults (11.06). Four articles[94, 101, 103, 104] reported on timing of AEs in 58 children, resulting in incidence rates of sequelae, major and minor AEs of 24.9, 24.14 and 18.97 cases in 100 patients within the first 6 months post-surgery. Two articles reported F/U times longer than 6 months: While Hultcrantz et al. 2015[101] reported 2 abutment exchanges in 10 children between 6 and 12 months, Doshi et al. 2013[94] reported no further AEs or sequelae among 8 children up to 36 months post-OP.

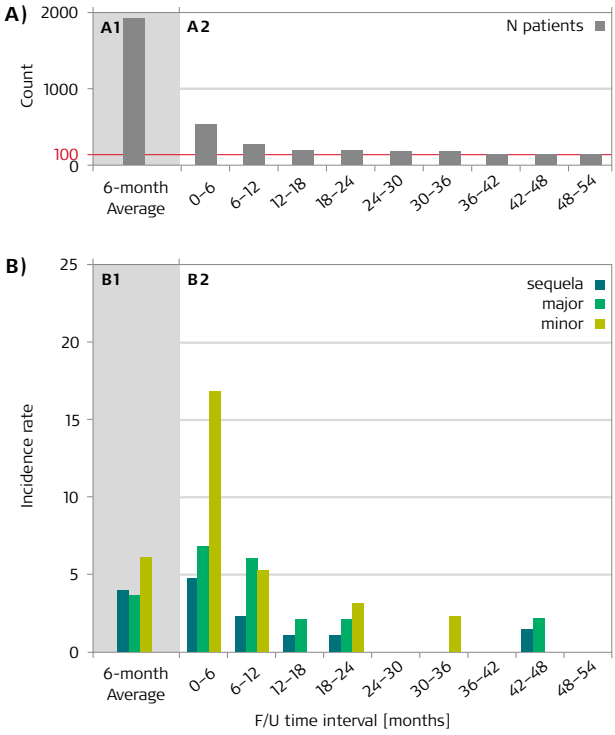

Figure 8: Incidence rate (cases in 100 patients and 6 months) of adverse events and sequelae after Baha Connect surgery. A) Pooled number of patients followed-up across studies reporting mean F/U time (A1) and across studies reporting time-to-event (A2). B) Average incidence rates per 6 months, calculated from 37 articles reporting mean F/U time (B1) and incidence rates for consecutive 6-month intervals, calculated from 16 articles reporting time-to-event (B2).

Table 5: Adverse events and sequelae observed at incidence rates above 1 case in 100 patients, within one year after Baha Connect surgery. (Inc. rate = 12-month incidence rate)

	Event name	Type	Inc. rate
1	Holgers grade 1	minor	13.83
2	Holgers grade 2	minor	3.60
3	Holgers grade 3	major	3.60
4	Revision surgery	sequela	3.60
5	Implant extrusion or fixture loss	major	1.70
6	Mild to moderate pain	minor	1.52
7	Swelling	minor	1.52
8	Trauma to the implant	major	1.33
9	Abutment exchange	sequela	1.33
10	Skin overgrowth	major	1.14
11	Holgers grade 4	major	1.14

4. MIDDLE EAR IMPLANTS

4.1. VIBRANT SOUNDBRIDGE (MED-EL)

Pooled patient population

Sixty-five articles reported on safety outcomes after VIBRANT SOUNDBRIDGE implantation in 1695 patients. Of these, 10 articles[116-125] did not report any time horizon for AE occurrence or patient follow-up and were therefore excluded from further analyses. In the remaining 55 articles[123, 126-180], 357 adverse events (in 223 patients) and 195 sequelae (in 158 patients) were reported in a total population of 1437 patients (Figure 9 – A1) over an average F/U time of 38.8 months. Twenty-seven articles[128, 130-132, 134, 135, 138, 139, 141, 144-150, 152, 154, 158, 161, 162, 166, 168, 174, 176, 178, 179] reported time-to-event for 78 AEs and 39 sequelae in a population of 424 patients (Figure 9 – A2) over F/U times of up to 60 months.

Frequency of adverse events

The average incidence rates of sequelae, major and minor AEs were 2.1, 1.32 and 2.52 cases in 100 patients and 6 months, respectively (Figure 9 – B1). Patients experiencing AEs had on average 1.6 AEs or 1.23 sequelae over their F/U period.

AEs (both minor and major each 4.95 cases) and sequela (8.73 cases) were highest within the first 6 months post-surgery and levelled out to below 2 cases in 100 patients from 6-12 months onward (Figure 9 – B2). The apparent increase after 36 months overlapped with a drop in sample size below 100 patients.

Types of adverse events

Overall, 46 types of adverse events and 7 types of sequelae were reported in the reviewed literature. The complete list of AEs is given in Appendix 3. Table 6 lists all adverse events and sequelae that were recorded at frequencies above 1 case in 100 patients within the first year after VIBRANT SOUNDBRIDGE surgery.

Safety in children vs. adults

Five articles [133, 147, 156, 161, 168] reported on safety in 76 children over a mean F/U time of 13.25 months. No sequelae or major AEs were reported. The incidence rate of minor AEs was 1.79 cases in 100 children per 6 months, well comparable to 2.58 cases in the adult population.

Three of these articles reported on timing of AEs in 45 children, resulting in incidence rates of sequelae, major and minor AEs of 0.0, 6.67 and 0.0 cases in 100 children within the first 6 months post-surgery. No further AEs were observed up to 18 months post-surgery by Roman et al. 2012 [168] and up to 65 months (mean: 42 months) by Mandala et al. 2011 [161].

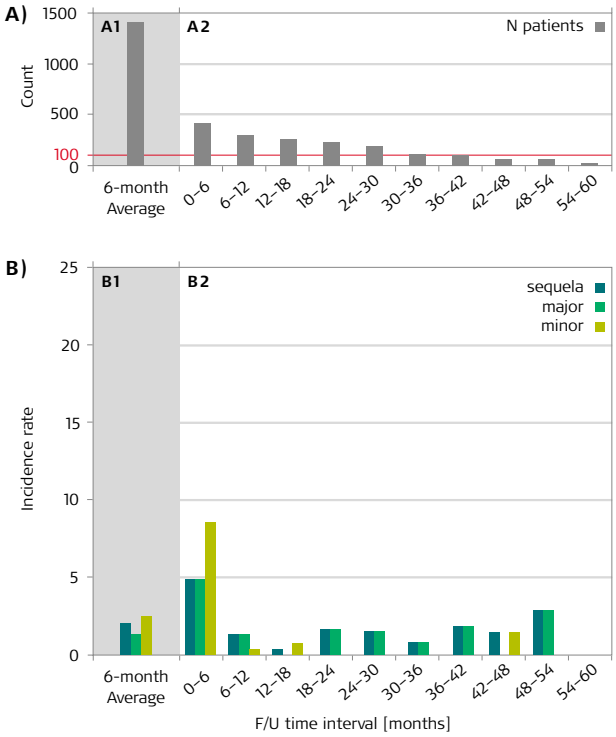

Figure 9: Incidence rate (cases in 100 patients and 6 months) of adverse events and sequelae after VIBRANT SOUNDBRIDGE surgery. A) Pooled number of patients followed-up across studies reporting mean F/U time (A1) and across studies reporting time-to-event (A2). B) Average incidence rates per 6 months, calculated from 55 articles reporting mean F/U time (B1) and incidence rates for consecutive 6-month intervals, calculated from 27 articles reporting time-to-event (B2).

Table 6: Adverse events and sequelae observed at incidence rates above 1 case in 100 patients within one year after VIBRANT SOUNDBRIDGE surgery. (Inc. rate = 12-month incidence rate)

	Event name	Type	Inc. rate
1	Revision surgery	sequela	3.07
2	Dizziness or vertigo	minor	2.12
3	FMT dislocation or other loss of coupling efficiency	major	2.12
4	Skin laceration in EEC	minor	1.42
5	Explantation (for medical reason, no benefit or on patient's request)	sequela	1.37
6	Reimplantation	sequela	1.27
7	Device failure	major	1.04

4.2. Carina (Cochlear Ltd.)

Pooled patient population

Twelve articles[167, 181-191] reported on safety outcomes after Carina surgery in 400 patients. Of these, 4 articles [167, 186, 190, 191] did not report any time horizon for AE occurrence or patient follow-up and were therefore excluded from further analyses. Six articles reported 76 adverse events (in 74 patients) and 31 sequelae (in 31 patients) in a total population of 183 patients (Figure 10 – A1) over an average F/U time of 26.3 months. Eight articles [181-185, 187-189] reported time-to-event for 121 AEs and 86 sequelae in a population of 246 patients (Figure 10 – A2) over F/U times of up to 72 months.

Frequency of adverse events

The average incidence rates of sequelae, major and minor AEs were 3.87, 3.62 and 5.86 cases in 100 patients and 6 months, respectively (Figure 10 – B1). Patients experiencing AEs had on average 1.27 AEs or 1.0 sequela over their F/U period.

Incidence rates of sequelae, major and minor AEs were highest within the first 6 months post-surgery (15.45, 15.04 and 8.94 cases, respectively). Sequelae and major AEs both levelled out at 2.48 cases between 24 and 36 months post-surgery (Figure 10 – B2). Elevated rates seen at longer F/U intervals were likely biased due to low sample size. No minor AEs were reported at F/U longer than 18 months. This was likely due to publication bias since most articles reporting on long-term use of Carina focused exclusively on device failure and removal rates.

Types of adverse events

Overall, 25 types of adverse events and 5 types of sequelae were reported in the reviewed literature. The complete list of AEs is given in Appendix 3. Table 7 lists all adverse events and sequelae that were recorded at frequencies above 1 case in 100 patients within the first year after Carina surgery.

Safety in children vs. adults

The Carina is not approved for children below 14 years and all of the included articles exclusively reported on safety outcomes in adults.

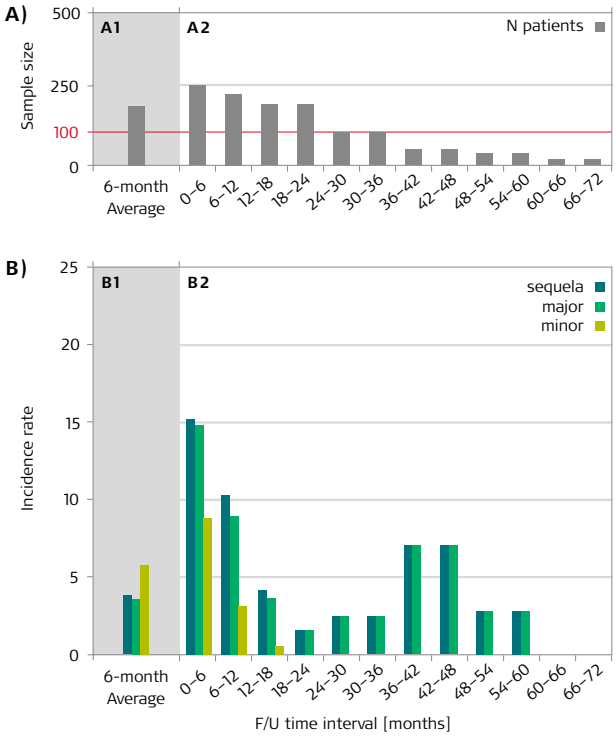

Figure 10: Incidence rate (cases in 100 patients and 6 months) of adverse events and sequelae after Carina surgery. A) Pooled number of patients followed-up across studies reporting mean F/U time (A1) and across studies reporting time-to-event (A2). B) Average incidence rates per 6 months, calculated from 6 articles reporting mean F/U time (B1) and incidence rates for consecutive 6-month intervals, calculated from 8 articles reporting time-to-event (B2).

Table 7: Adverse events and sequelae observed at incidence rates above 1 case in 100 patients within one year after Carina surgery. (Inc. rate = 12-month incidence rate)

	Event name	Type	Inc. rate
1	Explantation (medical reason, no benefit, patient's request)	sequela	20.42
2	Implant/device failure	major	10.28
3	Infection	major	4.93
4	Increased charging times beyond 1.5 hours	minor	3.18
5	Non-user for technical reason	sequela	2.13
6	Revision surgery	sequela	2.13
7	Conductive hearing loss	minor	1.63
8	Total sensorineural hearing loss	major	1.63
9	Device extrusion, displacement or migration	major	1.36
10	Transducer contact loss	major	1.27
11	Middle ear effusion	minor	1.22
12	AC thresholds decreased post-op	minor	1.22

4.3. Esteem (Envoy Medical)

Pooled patient population

Seven articles[192-198] reported on safety outcomes after Esteem surgery in 190 patients. Of these, 3 articles[195, 197, 198] did not report any time horizon for AE occurrence or patient follow-up and were therefore excluded from further analyses. Three articles[192, 194, 196] reported 117 adverse events (in 61 patients) and 20 sequelae (in 11 patients) in a total population of 74 patients (Figure 11 – A1) over an average F/U time of 13.59 months. Three articles [192, 193, 196] reported time-to-event for 33 AEs and 19 sequelae in a population of 30 patients (Figure 11 – A2) over F/U times of up to 30 months.

Frequency of adverse events

The average incidence rates of sequelae, major and minor AEs were 11.93, 7.75 and 62.03 cases in 100 patients and 6 months, respectively (Figure 11 – B1). Patients experiencing AEs had on average 1.92 AEs or 1.82 sequelae over their F/U period.

Incidence rates of sequelae, major and minor AEs were highest within the first 6 months post-surgery (56.67, 36.67 and 66.67 cases, respectively). Sequelae and major AEs both levelled out at 10.0 cases between 6 and 18 months post-surgery (Figure 11 – B2). No minor AEs were reported at F/U longer than 6 months.

Incidence rates estimated for the Esteem were based on very few samples and may therefore not be reliable. However, rates of AEs and sequelae appeared highly elevated compared to other MEIs. It should be noted that Shohet and colleagues[198] reported AEs and sequelae in a patient collective (N = 51) followed-up for up to 7 years. However, the authors failed to report mean F/U time or time-to-event for AEs (though time-to-event for battery changes is given), and therefore their data could not be analyzed within this framework.

Types of adverse events

Overall, 18 types of adverse events and 4 types of sequelae were reported in the reviewed literature. The complete list of AEs is given in Appendix 3. Table 8 lists all adverse events and sequelae that were recorded at frequencies above 1 case in 100 patients within the first year after Esteem surgery.

Safety in children vs. adults

The Esteem is not approved for use in patients below the age of 18 years.

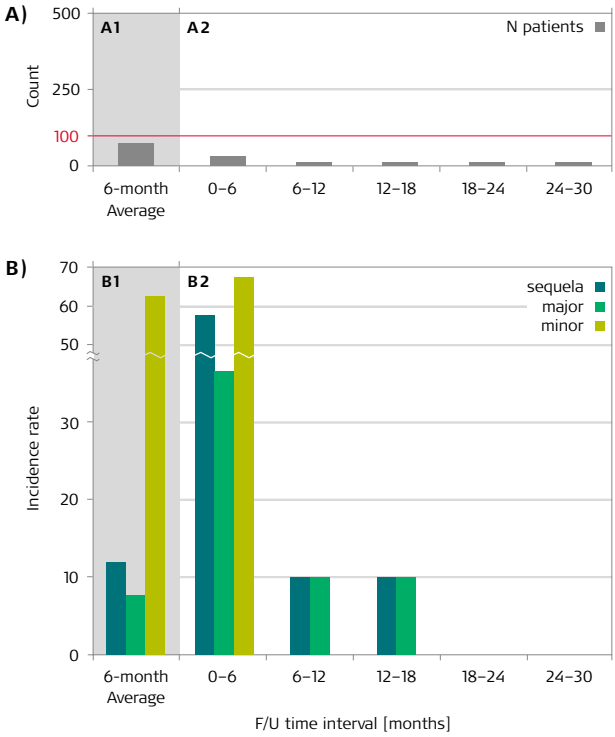

Figure 11: Incidence rate (cases in 100 patients and 6 months) of adverse events and sequelae after Esteem surgery. A) Pooled number of patients followed-up across studies reporting mean F/U time (A1) and across studies reporting time-to-event (A2). B) Average incidence rates per 6 months, calculated from 3 articles reporting mean F/U time (B1) and incidence rates for consecutive 6-month intervals, calculated from 3 articles reporting time-to-event (B2).

Table 8: Adverse events and sequelae observed at incidence rates above 1 case in 100 patients within one year after Esteem surgery. (Inc. rate = 12-month incidence rate)

	Event name	Type	Inc. rate
1	Revision surgery	sequela	40.00
2	Chorda tympani sacrificed	minor	26.67
3	Explantations (medical reason, no benefit, patient's request)	sequela	16.67
4	Implant/device failure	major	13.33
5	Facial paresis/palsy/weakness	minor	10.00
6	Excessive bonegrowth in middle ear	major	10.00
7	Major wound infection	major	10.00
8	Poor or rapidly deteriorating benefit	major	10.00
9	Soreness or numbness in jaw or arm or hand	minor	6.67
10	No benefit / limited benefit / non-user	sequela	6.67
11	Taste disturbances / chorda tympani damage	minor	3.33
12	Headaches	minor	3.33
13	Wound healing difficulties	minor	3.33
14	Feedback noise	minor	3.33
15	Silicone allergy	minor	3.33
16	Middle ear fibrosis that impairs transducer function	major	3.33
17	Reimplantation	sequela	3.33

4.4. Maxum (Ototronix; formerly Soundtec)

Pooled patient population

Three articles[199-201] reported on safety outcomes after Maxum surgery in 194 patients. One[201] did not report any time horizon for AE occurrence or patient follow-up and was therefore excluded from further analyses. Two articles[199, 200] reported 49 adverse events (in 22 patients) in a total population of 126 patients Figure 12 – A1) over an average F/U time of 2.9 months. None of the articles reported time-to-event for AEs or sequelae.

Frequency of adverse events

Only minor AEs were reported, with an average incidence rate of 81.4 cases in 100 patients and 6 months, (Figure 12 – B1). Patients experiencing minor AEs had on average 2.23 AEs over their F/U period.

Data on the safety of the Maxum was very scarce and only covered the period immediately following surgery. No data on the mid- or long-term safety of this device was available.

Types of adverse events

Overall, 14 types of adverse events were reported in the reviewed literature. Since all these events presumably occurred within 12 months from surgery, AEs listed in Table 9 correspond to the full list given in Appendix 3.

Safety in children vs. adults

The Maxum is not approved for use in patients below the age of 18 years.

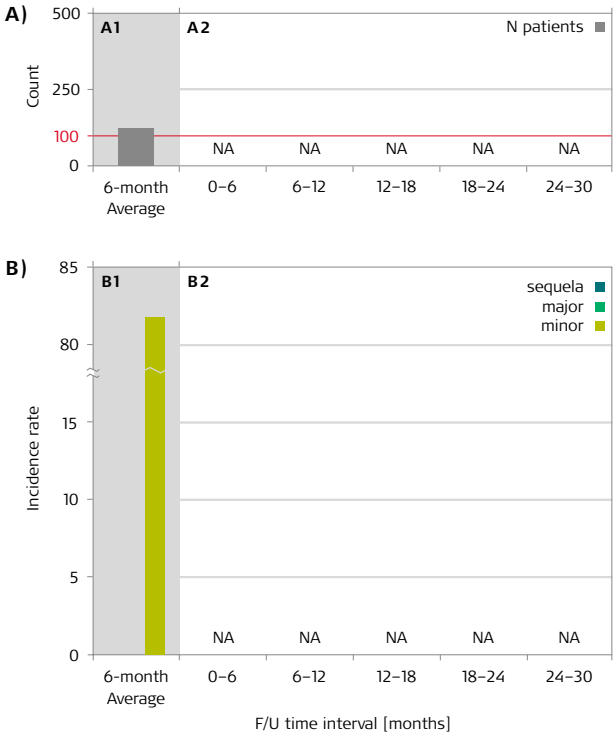

Figure 12: Incidence rate (cases in 100 patients and 6 months) of adverse events and sequelae after Maxum surgery. A) Pooled number of patients followed-up across studies reporting mean F/U time (A1) and across studies reporting time-to-event (A2). B) Average incidence rates per 6 months, calculated from 2 articles reporting mean F/U time (B1). None of the articles reported time-to-event for AEs (B2).

Table 9: Adverse events and sequelae observed at incidence rates above 1 case in 100 patients within one year after Maxum surgery. (Inc. rate = 12-month incidence rate)

	Event name	Type	Inc. rate
1	Ear pain	minor	26.59
2	Hematoma	minor	14.96
3	Tympanic membrane perforation	minor	8.31
4	Hematoma on the tympanic membrane	minor	8.31
5	Paresthesia / abnormal sensation of the ear	minor	3.32
6	Taste disturbances / chorda tympani damage	minor	3.32
7	Dizziness/vertigo	minor	3.32
8	Vomiting/nausea	minor	3.32
9	Transient hearing loss	minor	1.66
10	Tinnitus	minor	1.66
11	Otitis media	minor	1.66
12	Otitis externa	minor	1.66
13	Ear edema	minor	1.66
14	Ear eczema	minor	1.66

5. COMPARATIVE RESULTS

In order to put safety performances into perspective, device-specific incidence rates may be compared to each other. However, since these outcomes were not generated from studies directly comparing devices, some restrictions apply. Most importantly, incidence rates based on time-to-event (dataset 2) reported in sections 3 and 4 clearly show a negative association with F/U time. That is, less sequelae and AEs are reported in longer F/U intervals, irrespective of device or implant type. Therefore, incidence rates based on mean F/U (dataset 1) are likely biased, with longer mean F/U underestimating and shorter mean F/U overestimating actual rates. As a consequence, incidence rates based on mean F/U (dataset 1) should not be compared among devices, since they do not account for this effect of F/U time. On the other hand, incidence rates based on time-to-event (dataset 2) may be promptly compared among devices within same F/U intervals. For example, incidence rates in the first 12 months after surgery may be compared among all devices except the Maxum device (Figure 13).

Other parameters that potentially introduce some bias when comparing device-specific incidence rates may be related to study design or patient characteristics. Most studies in this field of research are, however, non-randomized single-cohort studies that compare post- to pre-treatment outcomes. Furthermore, patient cohorts may differ in terms of age, hearing loss indication, underlying pathology, or comorbidities. While separate incidence rates are given for children in many cases (see sections 3 and 4), data gathered here did not allow for a stratification by other confounding variables. These limitations should be kept in mind when comparing incidence rates among devices.

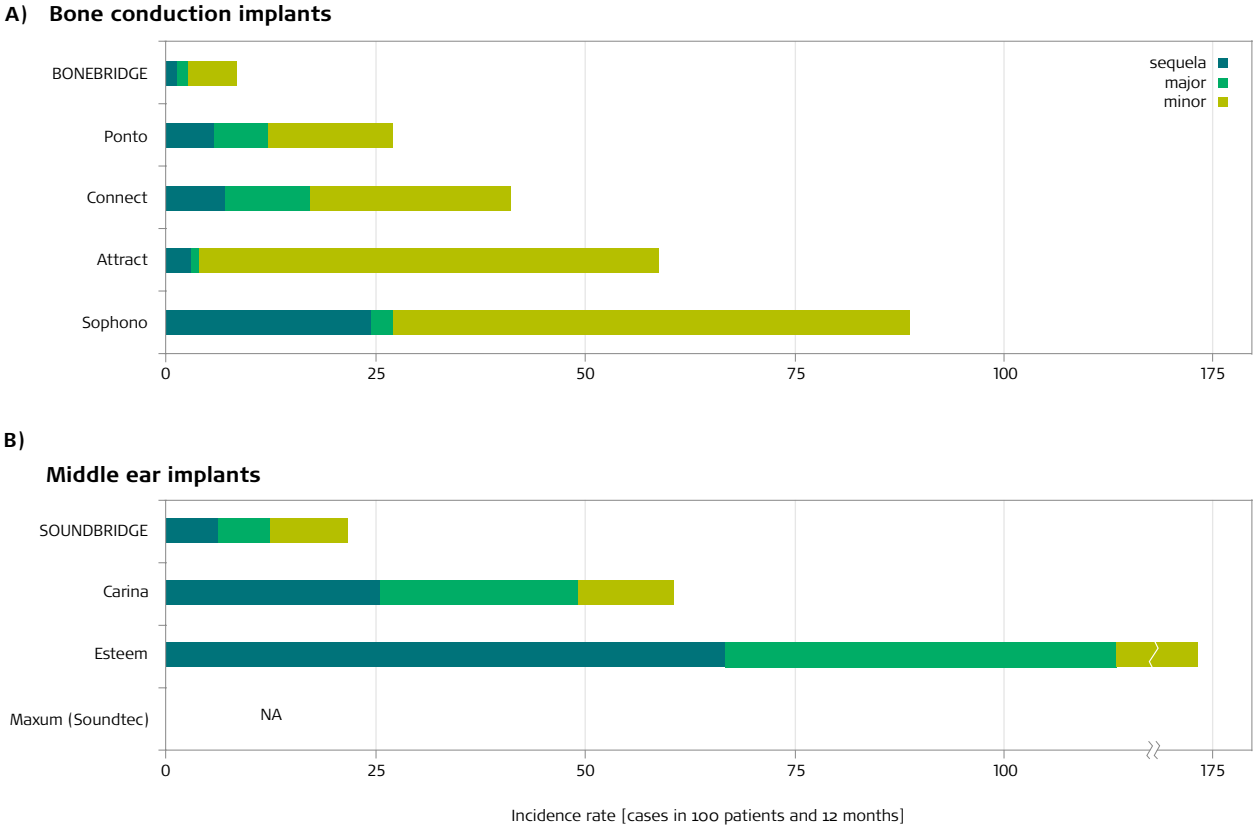

Figure 13: Comparison of incidence rates (based on time-to-event; dataset 2) in the first 12 months following surgery. No data were available for the Maxum device.

6. SUMMARY

The 5th revision of this White Paper introduced some major updates with regards to data analysis and visualization. Providing incidence rates for consecutive 6-month F/U intervals, enabled a more detailed picture of device-specific safety profiles over time. Among all devices, most AEs and sequelae occurred within 6 months after surgery, and rates generally decreased with longer F/U intervals. This pattern indicates that both, sequelae and AEs were rather associated with implant surgery than with device use, irrespective of the device. Within comparable timeframes, however, incidence rates differed among devices in terms of highest level, speed of post-surgical decrease and long-term level. As recently shown by Schwab and colleagues[3], MED-EL implants are confirmed as safest implants among current implantable treatment options.

7. DEFINITIONS

The following definitions apply within the framework of this document only.

Active implant	Implant including a battery-powered actuator. The battery doesn't need to be part of the implant.
Actuator	The motion-generating component of BCI or MEI systems that stimulates the residual hearing pathway by converting electrical into mechanical energy (sometimes referred to as transducer).
Direct-Drive	Stimulation via direct contact of the actuator with the target structure (e.g. mastoid, ossicles, round/oval window)
Dysesthesia	Abnormal, unpleasant sensation of the skin.
Edema	Mild to severe swelling caused by fluid retention.
Erythema	Skin redness occurring with any skin injury, infection, or inflammation.
Holgers grade	Grading system [202] for soft tissue reactions associated with bone-anchored hearing aids: 0 = No skin reaction/slightly red >1.00 mm from the implant 1 = red 1 mm or more from the implant 2 = red and moist 3 = red, moist, granulation tissue 4 = extensive soft-tissue reaction resulting in implant removal
Incidence rate	Frequency measure of adverse events or sequelae, expressed in cases per 100 patients and time unit.
Laceration	Irregular wound (not incision) caused by some blunt trauma or tearing.
Major adverse event	Any unintended medical occurrence associated with implantation or usage of the device that results in prolonged or further hospitalization, surgical intervention or (non-temporary) inability to use the device.
Minor adverse event	Any untoward medical occurrence associated with implantation or usage of the device that is not deemed major.
Paresthesia	Abnormal sensation of the skin.
Sequela	Any action that is taken to treat a condition that is the consequence of a previous adverse event. E.g. a revision surgery (= sequela) is performed to treat a skin necrosis (= adverse event).
Skin Abscess	Local boil of pus with redness and swelling that is typically caused by bacterial infection.
Skin-Drive	Stimulation of the mastoid bone with a layer of skin precluding direct contact between actuator and the bone.
Transducer	see Actuator.
Ulceration	Lesion of the skin resulting from ischemia or inflammation. Often caused by persistent pressure on the skin.
Wound dehiscence	Rupture of the wound along a surgical incision

8. ABBREVIATIONS

AC	Air conduction
AE	Adverse event
BAHA	Bone-anchored hearing aid
BCI	Bone conduction implant
CHL	Conductive hearing loss
EEC	External ear canal
FMT	Floating mass transducer
F/U	Follow-up time
HL	Hearing loss
MEI	Middle ear implant
MHL	Mixed hearing loss
NA	No data available
SNHL	Sensorineural hearing loss

APPENDIX 1

Search terms

Bone conduct* OR bone anchor* OR Bonebridge OR BAHA OR Ponto OR Sophono OR „middle ear implant“ OR Vibroplasty OR „direct acoustic stimulation“ OR „floating mass transducer“ OR SOUNDBRIDGE OR Carina OR Esteem OR Soundtec OR Maxum AND Hearing impair* OR hearing loss OR deaf*

APPENDIX 2

Incidences of single AEs and sequelae w/o timing (dataset 3)

(Dev. = Device; AE = Adverse Event)

Dev. type	Dev. name	AE. class	AE. type	AE. name	Incidence (cases in 100 patients)
BCI	BONEBRIDGE	major	surgery	Postoperative cephalalgia due to newly formed fascia and bone between implant and dura	0,86
BCI	BONEBRIDGE	minor	device	feedback	3,45
BCI	BONEBRIDGE	minor	device	problems with magnet: AP falling off	3,45
BCI	BONEBRIDGE	minor	skin	skin redness or swelling	2,59
BCI	BONEBRIDGE	minor	skin	minor wound infection	1,72
BCI	Baha Attract	minor	skin	Holgers grade 1 (slight redness or crust formation) MINOR	4,35
BCI	Baha Attract	minor	pain or numbness	Numbness around the implant MINOR	34,78
BCI	Baha Connect	sequela	revision surgery	revision surgery_SEQUELA	11,47
BCI	Baha Connect	sequela	revision surgery	surgical intervention (no revision)	0,38
BCI	Baha Connect	sequela	explantation	explantation (medical reason, no benefit, patient's request)_SEQUELA	0,94
BCI	Baha Connect	sequela	abutment removal or exchange	abutment exchange_SEQUELA	7,71
BCI	Baha Connect	sequela	non-user	no or limited benefit_SEQUELA	1,69
BCI	Baha Connect	sequela	non-user	non-user for medical reason_SEQUELA	0,94
BCI	Baha Connect	sequela	reimplantation	reimplantation_SEQUELA	1,32
BCI	Baha Connect	major	system failure	osseointegration failure_MAJOR	2,26
BCI	Baha Connect	major	system failure	implant extrusion or fixture loss_MAJOR	1,69
BCI	Baha Connect	major	skin	bony overgrowth_MAJOR	0,94
BCI	Baha Connect	major	skin	Holgers grade 3 (infection or skin overgrowth which needs surgical revision)_MAJOR	3,76
BCI	Baha Connect	major	skin	Holgers grade 4 (extrusion of the implant because of infection)_MAJOR	2,44
BCI	Baha Connect	major	skin	skin overgrowth_MAJOR	1,69
BCI	Baha Connect	major	skin	wound dehiscence_MAJOR	0,38
BCI	Baha Connect	major	skin	skin flap failure_MAJOR	0,19
BCI	Baha Connect	major	skin	infection_MAJOR	0,38
BCI	Baha Connect	minor	skin	granulation tissue_MINOR	6,77
BCI	Baha Connect	minor	skin	skin reaction unspecified_MINOR	3,76
BCI	Baha Connect	minor	skin	skin overgrowth_MINOR	1,88
BCI	Baha Connect	minor	skin	Holgers grade 1 (slight redness or crust formation)_MINOR	5,26
BCI	Baha Connect	minor	skin	Holgers grade 2 (infection or skin overgrowth)_MINOR	7,33
BCI	Baha Connect	minor	skin	wound dehiscence_MINOR	4,89
BCI	Baha Connect	minor	skin	skinflap necrosis_MINOR	0,75
BCI	Baha Connect	minor	skin	skin thickening	6,39
BCI	Ponto	sequela	revision surgery	revision surgery	1,92
BCI	Ponto	sequela	abutment removal or exchange	abutment removed	1,92
BCI	Ponto	sequela	abutment removal or exchange	abutment exchange	1,92
BCI	Ponto	major	system failure	implant loss/osseointegration failure_MAJOR	1,92
BCI	Ponto	minor	surgery	prolonged wound healing	17,31
BCI	Ponto	minor	skin	inflammation	11,54
BCI	Ponto	minor	skin	Holgers grade 1 (slight redness or crust formation)	13,46
BCI	Ponto	minor	skin	Holgers grade 2 (infection or skin overgrowth)	3,85
BCI	Ponto	minor	skin	skin thickening	5,77
BCI	Sophono	minor	surgery	postoperative pain	2,86
BCI	Sophono	minor	surgery	intraoperative complications	2,86
BCI	Sophono	minor	skin	Soft tissue / skin overgrowth	2,86
BCI	Sophono	minor	skin	skin crust	2,86
BCI	Sophono	minor	pain or numbness	pressure discomfort	5,71
MEI	VIBRANT SOUNDBRIDGE	sequela	revision surgery	revision surgery	1,16

Dev. type	Dev. name	AE. class	AE. type	AE. name	Incidence (cases in 100 patients)
MEI	VIBRANT SOUNDBRIDGE	sequela	explantation	explantation (medical reason, no benefit, patient's request)	1,16
MEI	VIBRANT SOUNDBRIDGE	sequela	explantation	explantation (device failure)	0,78
MEI	VIBRANT SOUNDBRIDGE	sequela	non-user	non-user	1,16
MEI	VIBRANT SOUNDBRIDGE	sequela	reimplantation	reimplantation	0,78
MEI	VIBRANT SOUNDBRIDGE	major	surgery	FMT dislocation or other loss of coupling efficiency	0,78
MEI	VIBRANT SOUNDBRIDGE	major	surgery	postoperative SNHL_MAJOR	0,78
MEI	VIBRANT SOUNDBRIDGE	major	system failure	Device failure	0,78
MEI	VIBRANT SOUNDBRIDGE	major	skin	Skinflap necrosis	0,39
MEI	VIBRANT SOUNDBRIDGE	major	other	Patient falls out of criteria	0,78
MEI	VIBRANT SOUNDBRIDGE	minor	surgery	high frequency HL implanted ear	0,39
MEI	VIBRANT SOUNDBRIDGE	minor	skin	infection at implant site	1,16
MEI	VIBRANT SOUNDBRIDGE	minor	skin	seroma	0,39
MEI	VIBRANT SOUNDBRIDGE	minor	skin	skin emphysema	0,78
MEI	Carina	sequela	explantation	explantation (medical reason, no benefit, patient's request)_SEQUELA	39,29
MEI	Carina	major	device	cable breakage or problems with the battery	39,29
MEI	Esteem	sequela	revision surgery	revision surgeries SEQUELA	24,27
MEI	Esteem	sequela	revision surgery	battery change	10,68
MEI	Esteem	sequela	explantation	explantations (medical reason, no benefit, patient's request) SEQUELA	9,71
MEI	Esteem	sequela	non-user	NO BENEFIT / limited benefit / non-user	0,97
MEI	Esteem	major	surgery	Wound infection_MAJOR	0,97
MEI	Esteem	major	device	implant/device failure	0,97
MEI	Esteem	major	device	insufficient coupling	1,94
MEI	Esteem	major	device	battery life depletion	11,65
MEI	Esteem	major	skin	skin dehiscence	2,91
MEI	Esteem	major	patient	complete hearing loss	0,97
MEI	Esteem	major	patient	disturbed hearing sensation	0,97
MEI	Esteem	major	patient	ME fibrosis that impairs transducer function	1,94
MEI	Esteem	minor	surgery	incision site soreness	0,97
MEI	Esteem	minor	surgery	tenderness and drainage at incision site	0,97
MEI	Esteem	minor	surgery	neck pain	0,97
MEI	Esteem	minor	surgery	pain ns	0,97
MEI	Esteem	minor	surgery	dizziness/vertigo	0,97
MEI	Esteem	minor	surgery	facial paresis/palsy/weakness	4,85
MEI	Esteem	minor	surgery	facial numbness/tingling	0,97
MEI	Esteem	minor	surgery	tinnitus (not present before)	0,97
MEI	Esteem	minor	device	low performance	3,88
MEI	Esteem	minor	device	feedback noise	0,97
MEI	Esteem	minor	device	distortion	0,97
MEI	Esteem	minor	device	pain/discomfort around processor site	1,94
MEI	Esteem	minor	skin	postauricular skin “shrink wrapped” around the leads	0,97
MEI	Soundtec	minor	device	percepting magnet movement	51,47

APPENDIX 3

Incidence rates of single AEs and sequelae (dataset 1 &2)

(Dev. = Device; AE = Adverse Event)

Dev. type	Dev. name	AE. class	AE. type	AE. name	6-month Average	0–6 months	6–12 months	12–18 months	18–24 months	24–30 months	30–36 months	36–42 months	42–48 months	48–54 months	54–60 months	60–66 months	66–72 months
BCI	BONEBRIDGE	sequela	revision surgery	revision surgery	0,32	0,37	0,56	0,00	0,00	0,00							
BCI	BONEBRIDGE	sequela	revision surgery	reimplantation	0,32	0,00	0,00	0,00	0,00	1,64							
BCI	BONEBRIDGE	sequela	revision surgery	surgeries performed as sequela to complication (not revision surgery)	0,16	0,37	0,00	0,00	0,00	0,00							
BCI	BONEBRIDGE	major	surgery	Postoperative cephal-algia due to newly formed fascia and bone between implant and dura	0,16	0,00	0,56	0,00	0,00	0,00							
BCI	BONEBRIDGE	major	surgery	wound healing major infection	0,16	0,37	0,00	0,00	0,00	0,00							
BCI	BONEBRIDGE	major	system failure	sudden loss of benefit	0,16	0,00	0,00	0,00	0,00	1,64							
BCI	BONEBRIDGE	major	system failure	implant failure	0,16												
BCI	BONEBRIDGE	major	skin	wound dehiscence major	0,16	0,37	0,00	0,00	0,00	0,00							
BCI	BONEBRIDGE	minor	surgery	prolonged wound healing	0,32	0,74	0,00	0,00	0,00	0,00							
BCI	BONEBRIDGE	minor	device	headaches	0,16												
BCI	BONEBRIDGE	minor	device	problems with magnet: AP falling off	0,00	0,60	0,00	0,00	0,00	0,00							
BCI	BONEBRIDGE	minor	skin	unspecified skin reaction	0,32												
BCI	BONEBRIDGE	minor	skin	skin edema or he-matoma	0,16	0,37	0,00	0,00	0,00	0,00							
BCI	BONEBRIDGE	minor	skin	skin irritation (erythema) or itching	1,12	1,85	0,56	0,00	0,00	0,00							
BCI	BONEBRIDGE	minor	skin	seroma at implant site MINOR	0,16												
BCI	BONEBRIDGE	minor	skin	minor wound infection	0,96	1,85	0,00	0,00	0,00	0,00							
BCI	BONEBRIDGE	minor	pain or numbness	mild wound pain	0,16	0,37	0,00	0,00	0,00	0,00							
BCI	BONEBRIDGE	minor	pain or numbness	tinnitus	0,16												
BCI	Baha Connect	sequela	revision surgery	revision surgery	2,75	2,84	0,76	1,04	0,00	0,00	0,00	0,00	1,45	0,00			
BCI	Baha Connect	sequela	explantation	explantation (medical reason, no benefit, patient's request)	0,06	0,38	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	sequela	abutment removal or exchange	abutment removed	0,23	0,76	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	sequela	abutment removal or exchange	abutment exchange	0,76	0,19	1,14	0,00	1,04	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	sequela	non-user	no or limited benefit	0,09	0,38	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	sequela	non-user	non-user for medical reason	0,03	0,19	0,38	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	sequela	reimplantation	reimplantation	0,06												
BCI	Baha Connect	major	surgery	CSF fistula	0,01												
BCI	Baha Connect	major	system failure	osseointegration failure	0,10	0,57	0,00	0,52	0,52	0,00	0,00	0,00	0,72	0,00			
BCI	Baha Connect	major	system failure	abutment loss	0,11												
BCI	Baha Connect	major	system failure	implant extrusion or fixture loss	0,44	1,33	0,38	0,52	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	major	system failure	no benefit	0,11												

Dev. type	Dev. name	AE. class	AE. type	AE. name	6-month Average	0–6 months	6–12 months	12–18 months	18–24 months	24–30 months	30–36 months	36–42 months	42–48 months	48–54 months	54–60 months	60–66 months	66–72 months
BCI	Baha Connect	major	system failure	feedback problems (reason to stop uing device)	0,00	0,19	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	major	device	trauma implant	0,21	0,95	0,38	0,00	0,52	0,00	0,00	0,00	1,45	0,00			
BCI	Baha Connect	major	skin	Holgers grade 3 (infection or skin over-growth which needs surgical revision)	0,67	2,08	1,52	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	major	skin	Holgers grade 4 (ext-rusion of the implant because of infection)	0,32	0,76	0,38	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	major	skin	hypertrophic scar	0,15												
BCI	Baha Connect	major	skin	skin or soft tissue complications	0,29												
BCI	Baha Connect	major	skin	skin overgrowth	0,77	0,38	0,76	1,04	1,04	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	major	skin	wound dehiscence	0,09												
BCI	Baha Connect	major	skin	skin flap failure	0,00	0,38	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	major	skin	skinflap necrosis	0,05	0,19	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	major	skin	infection	0,31												
BCI	Baha Connect	minor	surgery	healing difficulties	0,00	0,76	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	minor	surgery	swelling	0,00	1,52	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	minor	surgery	discharge at implant site	0,00	0,76	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	minor	surgery	bleeding from emissary vein	0,08	0,57	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	minor	surgery	intraoperative CSF leakage	0,01												
BCI	Baha Connect	minor	device	processor repair	0,14												
BCI	Baha Connect	minor	skin	granulation tissue	0,08												
BCI	Baha Connect	minor	skin	hematoma	0,03												
BCI	Baha Connect	minor	skin	erythema	0,06												
BCI	Baha Connect	minor	skin	infection	0,35												
BCI	Baha Connect	minor	skin	skin reaction unspecified	0,87												
BCI	Baha Connect	minor	skin	skin overgrowth	0,19	0,76	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	minor	skin	Holgers grade 1 (slight redness or crust formation)	0,47	6,63	7,20	0,00	2,60	0,00	2,27	0,00	0,00	0,00			
BCI	Baha Connect	minor	skin	Holgers grade 2 (infection or skin overgrowth)	2,35	3,60	0,00	0,00	0,52	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	minor	skin	skin hypertrophy	0,36												
BCI	Baha Connect	minor	skin	wound dehiscence	0,07												
BCI	Baha Connect	minor	skin	wound infection	0,11												
BCI	Baha Connect	minor	skin	soft tissue problems	0,55												
BCI	Baha Connect	minor	pain or numbness	chronic/persistent pain	0,02												
BCI	Baha Connect	minor	pain or numbness	periabutment paraesthesia	0,03												
BCI	Baha Connect	minor	pain or numbness	reduced skin sensitivity or numbness	0,17												
BCI	Baha Connect	minor	pain or numbness	periabutment paraesthesia	0,03	0,57	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Baha Connect	minor	pain or numbness	disturbance of sensibility	0,07												
BCI	Baha Connect	minor	pain or numbness	mild to moderate pain	0,00	1,52	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00			
BCI	Ponto	sequela	revision surgery	revision surgery	0,52	1,20	0,00	0,00	0,00								
BCI	Ponto	sequela	abutment removal or exchange	abutment removed	0,17	0,60	0,00	0,00	0,00								
BCI	Ponto	sequela	abutment removal or exchange	abutment exchange	1,92	2,99	0,98	0,00	0,00								
BCI	Ponto	major	system failure	implant loss/osseo-integration failure	1,22	2,10	0,49	0,00	0,00								
BCI	Ponto	major	system failure	abutment loss	0,17	0,30	0,00	0,00	0,00								

Dev. type	Dev. name	AE. class	AE. type	AE. name	6-month Average	0–6 months	6–12 months	12–18 months	18–24 months	24–30 months	30–36 months	36–42 months	42–48 months	48–54 months	54–60 months	60–66 months	66–72 months
BCI	Ponto	major	skin	Holgers grade 3 (infection or skin overgrowth which needs surgical revision)	1,57	2,40	0,49	0,00	0,00								
BCI	Ponto	major	skin	skin overgrowth	0,35	0,60	0,00	0,00	0,00								
BCI	Ponto	minor	surgery	dura mater exposed	0,52	0,90	0,00	0,00	0,00								
BCI	Ponto	minor	surgery	CSF leak	0,17	0,30	0,00	0,00	0,00								
BCI	Ponto	minor	surgery	bleeding	2,45	4,19	0,00	0,00	0,00								
BCI	Ponto	minor	surgery	prolonged wound healing	0,00	2,69	0,00	0,00	0,00								
BCI	Ponto	minor	surgery	insufficient skin healing after surgery	0,17	0,30	0,00	0,00	0,00								
BCI	Ponto	minor	surgery	fever	0,17	0,30	0,00	0,00	0,00								
BCI	Ponto	minor	skin	hematoma	0,17	0,30	0,00	0,00	0,00								
BCI	Ponto	minor	skin	inflammation	1,22	3,59	0,49	0,00	0,00								
BCI	Ponto	minor	skin	Holgers grade 1 (slight redness or crust formation)	12,95	20,66	2,44	0,00	0,00								
BCI	Ponto	minor	skin	Holgers grade 2 (infection or skin overgrowth)	4,72	7,19	1,46	0,00	0,00								
BCI	Ponto	minor	skin	keloid scar	0,17	0,00	0,00	0,00	3,23								
BCI	Ponto	minor	skin	wound dehiscence	1,05	1,80	0,00	0,00	0,00								
BCI	Ponto	minor	skin	persistent itch around the abutment	0,17	0,30	0,00	0,00	0,00								
BCI	Ponto	minor	pain or numbness	pain ns	5,77	9,28	0,98	0,00	0,00								
BCI	Ponto	minor	pain or numbness	reduced skin sensitivity/numbness	2,45	3,89	0,49	0,00	0,00								
BCI	Sophono	sequela	revision surgery	revision surgery	0,60	1,32	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	sequela	explantation	explantation (medical reason, no benefit, patient's request)	0,60	2,63	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	sequela	non-user	stopped using device	2,38	3,95	3,39	9,52	0,00	0,00	16,67						
BCI	Sophono	sequela	non-user	limited benefit or pausing needed	3,88	11,84	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	sequela	non-user	cosmetic reason	0,30	0,00	0,00	4,76	0,00	0,00	0,00						
BCI	Sophono	sequela	reimplantation	reimplantation	0,30	1,32	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	major	system failure	implant/device failure	0,60	2,63	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	surgery	intraoperative complications	0,60												
BCI	Sophono	minor	surgery	dura exposure	0,60	1,32	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	device	Device falling off the head	1,79	7,89	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	skin	skin breakdown	0,30	1,32	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	skin	hematoma ear	0,60	2,63	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	skin	Infection	0,60	2,63	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	skin	inflammation	0,60	2,63	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	skin	pressure ulcers	0,60	2,63	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	skin	Skin reaction (not further specified)	0,30	1,32	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	skin	breakdown	2,98	9,21	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	skin	Skinflap healing difficulties	0,60	2,63	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	skin	skin redness	0,00	1,32	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	skin	skin irritation due to magnet	0,30	1,32	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	skin	wound dehiscence	0,30	1,32	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	skin	Pressure necrosis	0,30	1,32	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	skin	Swelling	0,30	1,32	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	pain or numbness	pressure discomfort	2,68	7,89	5,08	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	pain or numbness	headaches	0,30	1,32	0,00	0,00	0,00	0,00	0,00						

Dev. type	Dev. name	AE. class	AE. type	AE. name	6-month Average	0–6 months	6–12 months	12–18 months	18–24 months	24–30 months	30–36 months	36–42 months	42–48 months	48–54 months	54–60 months	60–66 months	66–72 months
BCI	Sophono	minor	pain or numbness	pain at AP site	4,47	14,47	0,00	0,00	0,00	0,00	0,00						
BCI	Sophono	minor	pain or numbness	tingling of the skin	0,60	2,63	0,00	0,00	0,00	0,00	0,00						
BCI	Baha Attract	sequela	revision surgery	revision surgeries SEQUELA	0,63	0,60	0,00										
BCI	Baha Attract	sequela	explantation	explantations (medical reason, no benefit, patient's request) SEQUELA	0,85	1,21	0,00										
BCI	Baha Attract	sequela	non-user	non-user (unable to use or stopped using the device) SEQUELA	0,63	0,91	0,00										
BCI	Baha Attract	major	skin	Skin breakdown MAJOR	0,42	0,60	0,00										
BCI	Baha Attract	major	skin	Skin infection MAJOR	0,21	0,30	0,00										
BCI	Baha Attract	minor	device	Problems with magnet: difficulties finding correct balance to prevent slippage (too weak) or skin irritation (too strong) MINOR	2,54	3,02	1,67										
BCI	Baha Attract	minor	device	Trauma MINOR	0,21	0,30	0,00										
BCI	Baha Attract	minor	skin	Soft tissue problem (i.e. infection, inflammation, skin necrosis and/or scar hypertrophy) MINOR	0,21	0,30	0,00										
BCI	Baha Attract	minor	skin	Infection MINOR	0,63	0,91	0,00										
BCI	Baha Attract	minor	skin	Skin edema or erythema MINOR	1,27	1,51	0,83										
BCI	Baha Attract	minor	skin	Holgers grade 1 (slight redness or crust formation) MINOR	2,54												
BCI	Baha Attract	minor	skin	Seroma MINOR	0,21	0,30	0,00										
BCI	Baha Attract	minor	skin	Skin tenderness or redness	0,85	1,21	0,00										
BCI	Baha Attract	minor	pain or numbness	postoperative pain MINOR	8,67	11,48	0,00										
BCI	Baha Attract	minor	pain or numbness	Pain around the implant site, due to device use MINOR	2,54	3,63	0,00										
BCI	Baha Attract	minor	pain or numbness	Paresthesia / Dysesthesia (abnormal sensation) of the skin MINOR	3,39	2,42	5,00										
BCI	Baha Attract	minor	pain or numbness	Numbness around the implant MINOR	17,98	17,22	5,00										
MEI	VIBRANT SOUNDBRIDGE	sequela	revision surgery	revision surgery	0,87	3,07	0,00	0,00	0,84	1,04	0,83	0,93	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	sequela	revision surgery	surgeries performed as sequela to complication (not revision surgery)	0,06	0,24	0,33	0,00	0,00	0,00	0,00	0,93	1,47	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	sequela	explantation	explantation (medical reason, no benefit, patient's request)	0,26	0,71	0,66	0,00	0,42	0,52	0,00	0,00	0,00	1,47	0,00		
MEI	VIBRANT SOUNDBRIDGE	sequela	explantation	explantation (device failure)	0,29												
MEI	VIBRANT SOUNDBRIDGE	sequela	explantation	explantation (MRI, Radiotherapy)	0,03												
MEI	VIBRANT SOUNDBRIDGE	sequela	non-user	non-user	0,16	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	1,47	0,00		
MEI	VIBRANT SOUNDBRIDGE	sequela	reimplantation	reimplantation	0,42	0,94	0,33	0,00	0,42	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	major	surgery	FMT dislocation or other loss of coupling efficiency	0,58	2,12	0,00	0,37	0,42	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	major	surgery	incus arrosion	0,01												
MEI	VIBRANT SOUNDBRIDGE	major	surgery	Damage during unrelated surgery	0,01												
MEI	VIBRANT SOUNDBRIDGE	major	surgery	VORP placed upside-down	0,01												
MEI	VIBRANT SOUNDBRIDGE	major	surgery	wire problems	0,04												
MEI	VIBRANT SOUNDBRIDGE	major	surgery	postoperative SNHL	0,02	0,47	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		

Dev. type	Dev. name	AE. class	AE. type	AE. name	6-month Average	0–6 months	6–12 months	12–18 months	18–24 months	24–30 months	30–36 months	36–42 months	42–48 months	48–54 months	54–60 months	60–66 months	66–72 months
MEI	VIBRANT SOUNDBRIDGE	major	system failure	Device failure	0,34	0,71	0,33	0,00	0,42	0,00	0,00	0,00	0,00	1,47	0,00		
MEI	VIBRANT SOUNDBRIDGE	major	device	pain complaint	0,03												
MEI	VIBRANT SOUNDBRIDGE	major	device	Trauma	0,01												
MEI	VIBRANT SOUNDBRIDGE	major	skin	skin infection	0,01												
MEI	VIBRANT SOUNDBRIDGE	major	skin	EAC skin dehiscence revision (wire problems)	0,03												
MEI	VIBRANT SOUNDBRIDGE	major	patient	myringoplasty	0,01												
MEI	VIBRANT SOUNDBRIDGE	major	patient	Cholesteatoma	0,01												
MEI	VIBRANT SOUNDBRIDGE	major	patient	FMT fixed by extensive fiber tissue	0,03	0,24	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	major	patient	tympanic perforation exposing the FMT	0,01	0,24	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	major	patient	hematoma requiring revision surgery	0,01												
MEI	VIBRANT SOUNDBRIDGE	major	patient	infection and extrusion of internal coil	0,01	0,00	0,33	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	major	patient	infection of the cavity	0,03	0,24	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	major	patient	otosclerosis	0,01	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	1,47	0,00		
MEI	VIBRANT SOUNDBRIDGE	major	patient	collapse of the ear canal	0,01	0,24	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	major	other	Patient falls out of criteria	0,09	0,24	0,66	0,00	0,42	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	major	other	major complication, not specified	0,03	0,24	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	minor	surgery	tinnitus	0,08												
MEI	VIBRANT SOUNDBRIDGE	minor	surgery	aural fullness	0,47												
MEI	VIBRANT SOUNDBRIDGE	minor	surgery	conductor wire extrusion	0,14	0,71	0,00	0,74	0,42	1,55	0,83	1,87	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	minor	surgery	deterioriation in he-aring sensitivity after surgery	0,10												
MEI	VIBRANT SOUNDBRIDGE	minor	surgery	facial nerve damage or temporal facial palsy	0,04	0,71	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	minor	surgery	incus erosion	0,01												
MEI	VIBRANT SOUNDBRIDGE	minor	surgery	insuffiecient coupling FMT MINOR	0,04												
MEI	VIBRANT SOUNDBRIDGE	minor	surgery	pain at implant site	0,04	0,71	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	minor	surgery	postoperative SNHL, minor	0,26	0,71	0,00	0,00	0,00	0,52	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	minor	surgery	TM perforation	0,03	0,47	0,00	0,00	0,00	0,00	0,00	0,00	1,47	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	minor	surgery	skin laceration in EEC	0,06	1,42	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	minor	surgery	tinnitus that was not present before	0,02	0,47	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	minor	surgery	taste disturbances or chorda tympani damage	0,10	0,94	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	minor	device	AP failure/change	0,04	0,00	0,33	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	minor	device	discomfort at implant site	0,02	0,24	0,00	0,37	0,00	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	minor	skin	hematoma ear	0,02												
MEI	VIBRANT SOUNDBRIDGE	minor	skin	infection at implant site	0,06	0,24	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	minor	skin	prolongel wound healing	0,01	0,24	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		
MEI	VIBRANT SOUNDBRIDGE	minor	skin	skin reaction unspecified	0,20												
MEI	VIBRANT SOUNDBRIDGE	minor	pain or numbness	dizziness or vertigo	0,26	2,12	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00		

Dev. type	Dev. name	AE. class	AE. type	AE. name	6-month Average	0–6 months	6–12 months	12–18 months	18–24 months	24–30 months	30–36 months	36–42 months	42–48 months	48–54 months	54–60 months	60–66 months	66–72 months
MEI	VIBRANT SOUNDBRIDGE	minor	other	external auditory canal fistula	0,01												
MEI	VIBRANT SOUNDBRIDGE	minor	other	headaches	0,06												
MEI	VIBRANT SOUNDBRIDGE	minor	other	loss of AP	0,01												
MEI	VIBRANT SOUNDBRIDGE	minor	other	non specified minor complication	0,40												
MEI	Carina	sequela	revision surgery	revision surgery	0,75	1,22	0,91	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	sequela	explantation	explantation (medical reason, no benefit, patient's request)	2,37	11,79	8,64	3,70	1,59	4,95	14,29	5,71	0,00	0,00	0,00	0,00	0,00
MEI	Carina	sequela	non-user	non-user for medical reason	0,00	0,41	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	sequela	non-user	non-user for technical reason	0,50	1,22	0,91	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	sequela	reimplantation	reimplantation	0,25	0,41	0,00	0,53	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	major	surgery	chorda tympani sectioned	0,25	0,81	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	major	surgery	wound dehiscence	0,50	0,41	0,45	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	major	surgery	total sensorineural hearing loss	0,00	1,63	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	major	surgery	opening of the dura	0,12	0,00	0,45	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	major	system failure	transducer failure	1,00												
MEI	Carina	major	system failure	transducer contact loss	0,12	0,81	0,45	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	major	system failure	implant/device failure	0,50	5,28	5,00	3,70	1,59	2,48	2,48	7,14	7,14	2,86	2,86	0,00	0,00
MEI	Carina	major	device	Device extrusion/ displacement/migration	0,37	0,00	1,36	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	major	device	persistent feedback requiring mic repositioning	0,12	0,81	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	major	device	trauma to implant site	0,12	0,41	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	major	device	inability to charge or establish communication	0,25	0,00	0,91	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	major	skin	infection	0,25	4,47	0,45	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	minor	surgery	post-op SNHL /decrea-se in BC thresholds	0,00	0,81	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	minor	surgery	tinnitus (not present before)	0,12	0,81	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	minor	surgery	conductive hearing loss	0,50	1,63	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	minor	surgery	AC thresholds decreased post-op	0,00	1,22	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	minor	surgery	middle ear effusion	0,37	1,22	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	minor	surgery	postoperative hemotympanum	6,24												
MEI	Carina	minor	device	persistent feedback problems	2,99	0,00	0,00	0,53	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	minor	device	increased charging times beyond 1.5 hours	0,87	0,00	3,18	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	minor	device	hair friction perceived by implanted microphone	0,00	0,81	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	minor	pain or numbness	pain or discomfort	0,62												
MEI	Carina	minor	pain or numbness	dizziness/vertigo	0,00	0,41	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	minor	pain or numbness	fullness or pressure sensation	0,25	0,81	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Carina	minor	pain or numbness	lightheadedness	0,12	0,41	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
MEI	Esteem	sequela	revision surgery	revision surgeries SEQUELA	5,37	30,00	10,00	0,00	0,00	0,00							
MEI	Esteem	sequela	explantation	explantations (medical reason, no benefit, patient's request) SEQUELA	2,98	16,67	0,00	10,00	0,00	0,00							

Dev. type	Dev. name	AE. class	AE. type	AE. name	6-month Average	0–6 months	6–12 months	12–18 months	18–24 months	24–30 months	30–36 months	36–42 months	42–48 months	48–54 months	54–60 months	60–66 months	66–72 months
MEI	Esteem	sequela	non-user	NO BENEFIT / limited benefit / non-user	3,58	6,67	0,00	0,00	0,00	0,00							
MEI	Esteem	sequela	reimplantation	reimplantation	0,00	3,33	0,00	0,00	0,00	0,00							
MEI	Esteem	major	surgery	Wound infection	1,79	10,00	0,00	0,00	0,00	0,00							
MEI	Esteem	major	device	implant/device failure	2,39	13,33	0,00	0,00	0,00	0,00							
MEI	Esteem	major	device	poor or rapidly deteriorating hearing gain	0,60	10,00	0,00	10,00	0,00	0,00							
MEI	Esteem	major	patient	ME fibrosis that impairs transducer function	2,39	3,33	0,00	0,00	0,00	0,00							
MEI	Esteem	major	patient	excessive bonegrowth in ME	0,60	0,00	10,00	0,00	0,00	0,00							
MEI	Esteem	minor	surgery	headaches	0,60	3,33	0,00	0,00	0,00	0,00							
MEI	Esteem	minor	surgery	pain ns	7,16												
MEI	Esteem	minor	surgery	soreness or numbness in jaw or arm or hand	1,19	6,67	0,00	0,00	0,00	0,00							
MEI	Esteem	minor	surgery	dizziness/vertigo	6,56												
MEI	Esteem	minor	surgery	facial palsy/weakness	3,58	10,00	0,00	0,00	0,00	0,00							
MEI	Esteem	minor	surgery	facial numbness/ tingling	0,60												
MEI	Esteem	minor	surgery	chorda tympany sacrificed	0,00	26,67	0,00	0,00	0,00	0,00							
MEI	Esteem	minor	surgery	taste disturbances / chorda tympani damage	15,51	3,33	0,00	0,00	0,00	0,00							
MEI	Esteem	minor	surgery	tinnitus (not present before)	5,96												
MEI	Esteem	minor	device	feedback noise	0,60	3,33	0,00	0,00	0,00	0,00							
MEI	Esteem	minor	skin	wound healing difficulties	0,00	3,33	0,00	0,00	0,00	0,00							
MEI	Esteem	minor	patient	Effusion ME	10,74												
MEI	Esteem	minor	patient	Silicone allergy	0,00	3,33	0,00	0,00	0,00	0,00							
MEI	Maxum (Soundtec)	minor	surgery	otitis media	1,66												
MEI	Maxum (Soundtec)	minor	surgery	tinnitus	1,66												
MEI	Maxum (Soundtec)	minor	surgery	Vomiting/Nausea	3,32												
MEI	Maxum (Soundtec)	minor	surgery	hematoma	14,96												
MEI	Maxum (Soundtec)	minor	surgery	dizziness/vertigo	3,32												
MEI	Maxum (Soundtec)	minor	surgery	hearing loss transient	1,66												
MEI	Maxum (Soundtec)	minor	surgery	taste disturbances / chorda tympani damage	3,32												
MEI	Maxum (Soundtec)	minor	device	Hematoma on the TM	8,31												
MEI	Maxum (Soundtec)	minor	device	tympanic membrane performation	8,31												
MEI	Maxum (Soundtec)	minor	skin	ear eczema	1,66												
MEI	Maxum (Soundtec)	minor	skin	ear edema	1,66												
MEI	Maxum (Soundtec)	minor	skin	otitis externa	1,66												
MEI	Maxum (Soundtec)	minor	pain or numbness	ear pain	26,59												
MEI	Maxum (Soundtec)	minor	pain or numbness	paresthesia / abnormal sensation of the ear	3,32												

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