Which Health Impacts of Medical Device Adverse Event Should Be Reported Immediately in Korea?

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Objective: Immediate medical device adverse event (MDAE) reporting indications of Korea include death, life-threatening, hospitalization (initial or prolonged), disability or permanent damage, and congenital malformation or abnormalities. With the advent of new codes from the International Medical Device Regulators Forum, a study was undertaken to explore the applicability of health impact codes as immediate MDAE reporting indications in the Republic of Korea.

Method: This domestic cross-sectional survey study was conducted for members from Medical Device Safety Information Monitoring Center in November 2019. For the annex F (health impact) codes defining health impact of an MDAE, we checked whether each code matched with the current indication of immediate reporting. Consensus was reached when ≥70% of experts agreed.

Results: A total of 28 experts from 19 centers responded to the survey. Of a total of 64 codes, 29 matched with the current indication. However, in an expert survey, 17 of 29 codes were not agreed for immediate reporting and 5 codes were found to be unmatched codes. For these 5 codes, experts agreed that they would need reporting immediately. Finally, only 17 codes achieved consensus for immediate reporting.

Conclusions: There is a discrepancy between the code matched to the current immediate MDAE reporting indication and experts’ consensus. Sufficient discussion and agreement would be needed to apply health impact codes for immediate reporting.

Key Words: medical device vigilance, patient safety, medical device adverse event, regulation, serious adverse event

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In modern health care practice, application areas and frequencies of medical device use have continuously expanded and grown. Medical device vigilance (MDV) is a crucial postmarket activity to secure patient safety from medical device-related hazard or harm.1 To achieve MDV’s goal, medical device adverse event (MDAE) information should be collected, evaluated, analyzed, and disseminated.1 Compiling incident databases from health care facilities within or among countries can provide a wealth of data. Analysis of such data may reveal patterns and highlight specific problems to be addressed to prevent recurring adverse events. However, effective information sharing requires common tools, common descriptors of events and causes, consistent use of terminology, and a structurally agreed framework.2 The International Medical Device Regulators Forum (IMDRF) is a major leading international organization for medical device regulatory harmonization and convergence.3 The adverse event working group (AE WG) of the IMDRF finalized and published “IMDRF terminologies for categorized MDAE reporting: terms, terminology structure, and codes” in March 2020.4 The Adverse Event Reporting terminology is composed of 4 sets of terminologies: medical device problem (annex A), cause investigation (annexes B, C, and D), health effects (annexes E and F), and components (annex G).

If the clinical impact of MDAE is serious, immediate reporting is needed. Appropriate subsequent remedial actions are essential for patient safety. The Global Harmonization Task Forces (GHTF) has defined serious adverse events (SAEs) as MDAEs that can lead to a death or a serious deterioration in health as follows: (1) life-threatening illness or injury, (2) permanent impairment of a body structure or body function, (3) inpatient hospitalization or prolongation of existing hospitalization, (4) medical or surgical intervention to prevent permanent impairment to body structure or a body function, or (5) fetal distress, fetal death, or a congenital abnormality/birth defect.5 The Global Harmonization Task Forces has also presented requirements for an immediate reporting about MDAEs that result in an unanticipated death or unanticipated serious injury or represent a serious public health threat (which results in imminent risk of death, serious injury, or serious illness that may require prompt remedial action).1 However, many medical device users who report MDAEs have difficulty in determining which cases are serious injuries that must be reported immediately. Therefore, we performed an expert survey about immediate MDAE reporting indication using IMDRF annex F codes defining health impact and describing consequences of the MDAE for the person affected.

METHODS

Voluntary or mandatory reporters of MDAE are mandated to fill up a domestic official MDAE reporting form with Korea Ministry of Food and Drug Safety (MFDS)’s AE codes including medical device problems, patient problems, and components related to MDAEs.6,7 Currently, health effects in MDAE reporting in Korea are required to select 1 of the following 8 types of MDAEs in the same way as U.S. Food and Drug Administration: death, life-threatening, disability or permanent damage, hospitalization (initial or prolonged), congenital anomaly/birth defects, required intervention to prevent permanent impairment/damage, other severe cases, and mild cases. In terms of timing of reporting, for some of these 8 types of health outcomes such as death, it is clear to recognize them for immediate reporting. However, for other types, it is difficult to

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determine whether it needs immediate reporting or not. In this regard, we thought that the IMDRF annex F, which consisted of codes for various health effects by a forum of voluntary medical device regulators from around the world, might be an appropriate tool to achieve consensus on which health effect should be subject to immediate reporting among stakeholders.8,9 We conducted an expert survey to select IMDRF annex F codes targeted for immediate MDAE reporting. This study was approved by the institutional review board of Soonchunhyang University Bucheon Hospital (2019-09-027-001). The requirement of informed consent was waived because of its retrospective nature.

IMDRF Annex F code and Current Immediate MDAE Reporting Indication

Annex F of the IMDRF provides a list of potential outcomes and consequences of the MDAE on the person affected.4 It can include final patient outcomes and/or interventions or procedures required as a result of the MDAE. Annex F has 64 codes having 3 levels to reflect the relationship to the parent/child and the body of nomenclature it belongs to.

Immediate MDAE reporting indications of Korea MFDS include death, life-threatening, hospitalization (initial or prolonged), disability or permanent damage, and congenital malformation or abnormalities.10 However, considering the global harmonization of MDAE, the following current immediate reporting indication in this study was defined based on GHTF/SG2/N54R8:2006 and IMDRF MDCE WG/N56FINAL:20191,5:

1) Death
2) A serious deterioration in health
   2.1) Life-threatening illness or injury
   2.2) Permanent impairment of a body structure or body function
   2.3) Inpatient hospitalization or prolongation of existing hospitalization
   2.4) Medical or surgical intervention to prevent permanent impairment to body structure or a body function
   2.5) Fetal distress, fetal death, a congenital abnormality, or birth defect
3) Serious public health threat

Annex F codes were classified according to whether they matched with the meaning of each immediate reporting indication. Level 2 and level 3 subcodes were classified according to their level 1 codes. For example, F12 (serious injury/illness/impairment) has 5 level 2 subcodes F1201–F1205. We considered that all 6 codes including F12 matched with the current immediate reporting indication “serious deterioration in health.”

Expert Opinion Survey and Prior Education

We enrolled members of Medical Device Safety Information Monitoring Center (MDSIMC) in 19 regional centers nationwide (Fig. 1). The MDSIMC was launched to enhance MDAE reporting in 2010. It was expanded to 19 centers in 2018.11 These regional centers are building a cooperative system with 120 health care institutions using satellite monitoring site in the surrounding area. The director and dedicated staff of all regional centers are obliged to attend a quarterly coalition meeting. This study was

| Characteristics                  | No. (%) |
|----------------------------------|---------|
| Sex                              |         |
| Male                             | 17 (60.7) |
| Age, y                           |         |
| 20–29                            | 1 (3.6)  |
| 30–39                            | 8 (28.6) |
| 40–49                            | 9 (32.1) |
| ≥50                              | 10 (35.7) |
| Career                           |         |
| Doctor                           | 12 (42.9) |
| Nurse                            | 4 (14.3)  |
| Medical technologist             | 5 (17.9)  |
| MDSIMC agent                     | 7 (25.0)  |
| Experience on MDAE, y            |         |
| <1                               | 7 (25.0)  |
| 1–5                              | 6 (21.4)  |
| 5–10                             | 11 (39.3) |
| ≥10                              | 4 (14.3)  |
| Total                            | 28       |
### TABLE 2. Adverse Event Terminology of IMDRF Annex F Codes Means Health Impact Describing the Consequences of the MDAE/Incident on the Person Affected

| IMDRF annex F code (n = 64) | Current Immediate AER Indication (Marched Indication No.) (n = 29) | Agreement as Immediate AER Indication by Experts | Achieve Consensus | No. Agreed Experts (%) |
|-----------------------------|---------------------------------------------------------------|-----------------------------------------------|-------------------|------------------------|
| F01 Change in therapeutic response | X | X | 11 (39.3) |
| F0101 Therapeutic response Decreased | X | X | 11 (39.3) |
| F0102 Therapeutic Response Increased | X | X | 3 (10.7) |
| F0103 Unexpected therapeutic effects | X | X | 8 (28.6) |
| F02 Death | O (1) | O | 27 (96.4) |
| F0201 Intrauterine fetal death | O (1), O (2.5) | O | 26 (92.9) |
| F03 Brain death | X | O | 26 (92.9) |
| F04 Delay to diagnosis | X | X | 9 (32.1) |
| F05 Delay to treatment/therapy | X | X | 14 (50.0) |
| F06 Disruption of subsequent medical procedure | X | X | 12 (42.9) |
| F07 Exacerbation of existing condition | X | O | 20 (71.4) |
| F08 Hospitalization or prolonged hospitalization | O (2.3) | X | 19 (67.9) |
| F0801 Intensive care | O (2.3) | O | 20 (71.4) |
| F09 Fetal harm | O (2.5) | O | 26 (92.9) |
| F10 Inadequate/inappropriate treatment or diagnostic exposure | X | X | 16 (57.1) |
| F1001 Absence of treatment | X | X | 16 (57.1) |
| F1002 Incompatible blood transfusion | X | O | 28 (100) |
| F1003 Missed dose | X | X | 12 (42.9) |
| F1004 Underdose | X | X | 11 (39.3) |
| F100401 Radiation underdose | X | X | 4 (14.3) |
| F1005 Overdose | X | O | 21 (75.0) |
| F100501 Radiation overdose | X | X | 19 (67.9) |
| F11 Minor injury/illness/impairment | X | X | 1 (3.6) |
| F12 Serious injury/illness/impairment | O (2) | O | 25 (89.3) |
| F1201 Chronic disease | O (2), O (2.2) | X | 5 (17.9) |
| F1202 Disability | O (2), O (2.2) | X | 14 (50.0) |
| F1203 Life-threatening illness or injury | O (2), O (2.1) | O | 27 (96.4) |
| F1204 Permanent impairment | O (2), O (2.2) | O | 24 (85.7) |
| F1205 Temporary impairment | O (2) | X | 8 (28.6) |
| F13 Misdiagnosis/misclassification | X | X | 12 (42.9) |
| F14 Prolonged episode of care | X | X | 6 (21.4) |
| F15 Recognized device or procedural complication | X | X | 6 (21.4) |
| F16 Reduction in life expectancy | X | X | 15 (53.6) |
| F17 Sedation | X | X | 11 (39.3) |
| F18 Rehabilitation | X | X | 12 (42.9) |
| F19 Surgical intervention | O (2.4) | X | 19 (67.9) |
| F1901 Additional surgery | O (2.4) | O | 20 (71.4) |
| F1902 Amputation | O (2.4) | O | 26 (92.9) |
| F1903 Device explantation | O (2.4) | O | 23 (82.1) |
| F1904 Device repositioning | O (2.4) | X | 16 (57.1) |
| F1905 Device revision or replacement | O (2.4) | X | 15 (53.6) |
| F1906 Modified surgical procedure | O (2.4) | X | 9 (32.1) |
| F1907 More complex surgery | O (2.4) | X | 15 (53.6) |
| F1908 Prolonged surgery | O (2.4) | X | 9 (32.1) |
| F1909 Surgical procedure delayed | O (2.4) | X | 7 (25.0) |
| F20 Serious public health threat | O (3) | O | 28 (100) |
| F21 Unexpected deterioration | X | X | 18 (64.3) |
| F22 Unexpected diagnostic intervention | X | X | 8 (28.6) |
| F2201 Biopsy | X | X | 6 (21.4) |
| F2202 Endoscopic procedure | X | X | 10 (35.7) |

(Continued next page)
TABLE 2. (Continued)

| IMDRF annex F code (n = 64) | Current Immediate AER Indication (Marched Indication No.) (n = 29) | Agreement as Immediate AER Indication by Experts |
|-----------------------------|---------------------------------------------------------------|-----------------------------------------------|
| Code                        | Term                                                          | Achieve Consensus | No. Agreed Experts (%) |
| F2203                       | Imaging required                                             | X                 | 6 (21.4)               |
| F2204                       | IVD testing                                                  | X                 | 5 (17.9)               |
| F23                         | Unexpected medical intervention                               | X                 | 13 (46.4)              |
| F2301                       | Additional device required                                    | O (2.4)           | X                     | 4 (14.3)               |
| F2302                       | Blood transfusion                                            | O (2.4)           | X                     | 16 (57.1)              |
| F2303                       | Medication required                                          | O (2.4)           | X                     | 12 (42.9)              |
| F2304                       | Prophylactic treatment                                       | O (2.4)           | X                     | 5 (17.9)               |
| F2305                       | Radiation therapy                                            | O (2.4)           | X                     | 10 (35.7)              |
| F2306                       | Resuscitation                                                | X                 | 26 (92.9)              |
| F24                         | Insufficient information                                     | X                 | 3 (10.7)               |
| F25                         | Unanticipated adverse device effect                          | O                 | 21 (75.0)              |
| F26                         | No health consequences or impact                              | X                 | X                     | 1 (3.6)                |
| F27                         | No patient involvement                                       | X                 | X                     | 2 (7.1)                |
| F28                         | Appropriate term/code not available                          | X                 | X                     | 6 (21.4)               |

Current immediate AER indication was determined based on GHTF/S2/N54R8:2006 and IMDRF MDCE WGN56FINAL:2019; adverse event that can lead to (1) a death; (2) a serious deterioration in the health of the subject leading to (2.1) life-threatening illness or injury, (2.2) permanent impairment of a body structure or body function, (2.3) inpatient hospitalization or prolongation of existing hospitalization, (2.4) medical or surgical intervention to prevent permanent impairment to body structure or a body function, or (2.5) fetal distress, fetal death, a congenital abnormality or birth defect or represent; and (3) a serious public health threat.

AER, adverse event reporting.

conducted through quarterly coalition meetings in 2019. We introduced the new IMDRF code system to active members of MDSIMC (March 2019), educated them on annex F codes (June 2019), and conducted discussion for cases (September 2019) after a trial application of annex F to actual MDAEs at each regional center. An expert opinion survey was conducted for participants of the MDSIMC coalition meeting in November 2019. In this survey, all terms of levels 1, 2, and 3 annex F codes and their definitions were provided simultaneously in Korean and English. We asked “Do you agree that this code is an indication that should be reported to MFDS immediately?” to members of MDSIMC.

Statistical Methods

Analysis of responses was conducted after blinding names of expert respondents. Consistent with other studies, consensus was considered to have been reached when ≥70% of experts agreed. Consensual values were summarized as number and percentage (%). Responses to questions were evaluated using SPSS Software (IBM SPSS Statistics 26; IBM Corp, Armonk, New York).

RESULTS

Characteristics of Survey Respondents

A total of 28 MDSIMC members responded to the survey. Their general characteristics are shown in Table 1. The most frequent career of responders was doctor (42.9%; 12/28). Those having 5 to 7 years of experience on MDAE accounted for the most (39.3%; 11/28).

Difference Between Current Immediate MDAE Reporting Indication and Expert Opinion

Of a total of 64 annex F codes, 29 codes matched with current immediate MDAE reporting indications (Table 2). There was a discrepancy between expert consensus and matching results for 22 codes. Although they did not match with the current indication, the following 5 codes needed immediate reporting according to agreement by experts: F03 (brain death), F07 (exacerbation of existing condition), F1002 (incompatible blood transfusion), F1005 (overdose), and F25 (unanticipated adverse device effect). On the other hand, 17 of 29 codes that matched with current indications failed to achieve a consensus that an immediate reporting was required, including F1201 (chronic disease), F1202 (disability), F1205 (temporary impairment), F08 (hospitalization or prolonged hospitalization), F19 (surgical intervention), F23 (unexpected medical intervention), and so on.

DISCUSSION

The establishment of a clear immediate MDAE reporting indication is important for MDV and appropriate subsequent remedial action for MDAE. The Medical Device Act of Korea declares that medical device handler (manufacturer, importer, repairer, seller, and lessor of medical devices and party or person who has opened medical facility) shall immediately report to the Korea MFDS when they encounter an SAE and keep records. According to Article 51 of the Enforcement Rules of the Medical Device Act, if death or life-threatening MDAEs including death or life-threatening, hospitalization (initial or prolonged), disability or permanent damage, and congenital anomaly or birth defect has occurred, it should be reported to the Korea MFDS within 7 or 15 days. There were a total of 22 code differences between the current indication and experts’ consensus in this study (Table 2). Based on this result, we thought that the indication of immediate reporting should not be limited to annex F codes matched with current indications. However, it is difficult to judge F08 (hospitalization or prolonged hospitalization), F12 (serious injury/illness/impairment), F19 (surgical intervention), F23 (unexpected medical intervention), and F25...
(unanticipated adverse device effect) without MDAE inspection. Thus, detailed guidance or explanation will be needed.

This study has several limitations. First, annex F code is not a causality-included concept. Because MDAE has a characteristic that is difficult to judge its causal relationship with medical devices,\textsuperscript{14} it is better to analyze the causal relationship retrospectively rather than having an MDAE reporting delay to evaluate this.

Second, our expert survey enrolled a small number of MDSIMC members in Korea, mainly institutional users. In 2006, Korea MFDS introduced the MDAE reporting system, which enforced MD manufacturers and medical facilities to report MDAE. However, the MDAE report in Korea has a small number because insufficient awareness of all parties. Therefore, Korea MFDS launched MDSIMC and domestic MDAE reporting from MDSIMC was increased from 7.8% in 2011 to 57.7% in 2019.\textsuperscript{11} Because other countries have similar or different situations according to their domestic laws and regulation, the judgment of experts in each country may differ from that in Korea.

Third, despite a prior education, it was impossible to rule out the possibility that differences in perception among experts affected results of this study. A study conducted on Asia-Pacific Economic Cooperation medical device regulators has reported that even if the international standard is well known, there is a difference in individual perception when it is applied in the field.\textsuperscript{15} There are various stakeholders related to medical device, including manufacturers, importers, distributors, retailers, institutional users, lay users, and concerned citizens groups.\textsuperscript{16,17} Differences in the perception of MDAE among occupations by medical staff have been reported.\textsuperscript{18} Medical device vigilance requires cooperation among all stakeholders.\textsuperscript{16} If SAE happens, all stakeholders should aid the report regardless of their roles. Therefore, besides applying internationally harmonized guidelines for reporting MDAE and having exchanges between countries, continuous education and training are needed to reduce the difference in perspective.

CONCLUSIONS

We explored which code would be suitable for immediate MDAE reporting among 64 IMDRF health impact discretion code (annex F). Because there was a discrepancy between the code matched to the current immediate MDAE reporting indication and experts’ consensus, it was determined that sufficient discussion and agreement would be needed to use the annex F code for an immediate reporting.

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