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Review

Regulatory approval review of transcatheter mitral valve repair – Difference in the indication between the USA and Japan

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ABSTRACT

The indication for MitraClip (Abbott Vascular, Santa Clara, CA, USA) in the USA is degenerative mitral regurgitation (DMR), but the Japanese indication includes both DMR and functional mitral regurgitation (FMR), in patients without severe left ventricular dysfunction. One of the reasons for this difference is that the Japanese Circulation Society submitted a formal request to the Japanese government for early approval of MitraClip for both DMR and FMR on the basis of unmet medical need for MR patients resistant to medical therapy, but at prohibitive risk for mitral valve surgery.

Here, we describe the regulatory approval review process of MitraClip in Japan. Clinical data from outside Japan indicated that MitraClip provides significant improvements from baseline in New York Heart Association Class and hospitalizations for heart failure due to the reduction of MR grade without adversely affecting long-term prognosis in FMR patients as well as DMR patients. Also, a Japanese domestic trial showed a favorable acute procedural success rate without serious adverse events with MitraClip in both DMR and FMR patients. Further, it is considered in Japan that improvement of MR mechanically is clinically important in both DMR and FMR, in patients without severe left ventricular dysfunction. On the basis of these considerations, the MitraClip was approved in Japan for indications of both DMR and FMR with preserved cardiac function in patients at prohibitive risk for mitral valve surgery.

Contents

Introduction

Over the past decade, the Japanese government has aimed to expedite the medical devices review process in order to secure timely access to innovative and safe devices for patients. The review time for new medical device regulatory approval in Japan has been dramatically shortened (average review time of new medical devices during 2005–2008: 21.1 months [1]; 60th percentile in 2015: 10.1 months [1]), providing better access for patients, as planned. Further, the difference in timings between regulatory approvals in the USA and those in Japan for the same devices (herein after called "device lag") has nearly been resolved due to several government policy initiatives [1].

However, there is still device lag in certain therapeutic categories, especially unmet medical needs. A recent example

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	Integrated High Risk Cohort*1 (EVEREST II HRR and Realism HR trial)	AVJ-514 (Japan Study)
Design	Single arm	
Target patients	Patients with significant symptomatic mitral regurgitation (MR ≥ 3) of either FMR or DMR etiology that were determined to be prohibitive risk for surgery.	
Patients number	351 pts (including E II HRR 78pts and Realism HR primary 273pts*1)	30pts
Sites	41 sites in US and Canada	6 sites in Japan

*1: EVEREST II HRR and Realism HR trial were prospective, multi-center, single-arm studies to evaluate the safety and effectiveness of the MitraClip in high surgical risk patients.

Fig. 1. Overview of clinical data for patients at high risk for mitral valve surgery. There are two clinical data sets on high-risk mitral valve surgery. One is the so-called "Integrated High Risk Cohort" which consists of the integrated EVEREST II High Risk Registry and EVEREST II Real World Expanded Multi-center Study of the MitraClip System Continued Access Study High Risk Cohort. The other is a Japanese domestic study designed to validate the extrapolation of non-Japanese clinical data to the Japanese medical environment. Both are prospective, multi-center, single-arm studies to evaluate the safety and effectiveness of the MitraClip in high surgical risk patients. Target patients were patients with significant symptomatic mitral regurgitation (mitral regurgitation ≥3) of either functional mitral regurgitation (FMR) or degenerative mitral regurgitation (DMR) etiology that were determined to be too high risk for surgery.

was EXCOR (Berlin Heart, Berlin, Germany), a pediatric external ventricular assist device (VAD), which is the same as the VAD for children approved in 2011 in the USA; there was a 4-year delay of its approval in Japan, compared to the US approval [1]. To improve the response to unmet medical needs, we have tried to conduct reviews based on not just non-clinical and clinical data, but rather a comprehensive evaluation including the physical effects, characteristics of medical devices, available guidelines, and scientific publications.

A recently approved medical device for an unmet medical need was the MitraClip NT system (Abbott Vascular, Santa Clara, CA, USA), which was approved in May 2016 in the USA and in October 2017 in Japan. Although the US indication includes only degenerative mitral regurgitation (DMR), that in Japan includes both DMR and functional mitral regurgitation (FMR), in patients without severe left ventricular dysfunction. Here, we explain how the risk–benefit balance of MitraClip for the indication of FMR in Japan was evaluated during the regulatory approval process.

Regulatory approval review of efficacy and safety of the MitraClip

The Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II randomized control trial [2] showed that the 5-year survival rate was almost the same between the MitraClip and mitral valve surgery [3] (MitraClip group: 81.2% vs. surgical group: 79.0%). However, the percentage of patients with MR grade ≦1 at 5 years was lower in the MitraClip and additionally, the 5-year reoperation-free rate to mitral valve surgery was also lower in the MitraClip group than in the surgical group (the percentage of patients with MR grade ≤1: MitraClip group: 50.0% vs. surgical group: 92.7%) (reoperation-free rate: MitraClip group: 74.3% vs. surgical group: 92.5%) [4]. From these results, it was difficult to conclude that the efficacy of the MitraClip treatment was equal to that of surgical treatment in patients who could undergo mitral valve surgery. Therefore, the sponsor developed the MitraClip for patients at high risk for mitral valve surgery.

There were two clinical data sets on the MitraClip in high-risk patients for mitral valve surgery. One was named the "Integrated High Risk Cohort", which was composed of the EVEREST II High Risk Registry [21] and the EVEREST II Real World Expanded Multi-center Study of the MitraClip System Continued Access Study High Risk Cohort; this was pivotal data for the Japanese submission [5]. The other was a Japanese domestic study designed to confirm the validity of extrapolation of the non-Japanese clinical data to the Japanese medical environment. The design was prospective, multi-center, and single arm, aiming to assess the safety and efficacy of the MitraClip at high-risk patients of mitral valve surgery in both cases. Target patients were those with significant symptomatic MR ≥3, either FMR or DMR, at high risk for mitral valve surgery (Fig. 1).

In the Integrated High Risk Cohort, the acute procedural success rate was 79.0% (83/105) in the DMR group, and 85.0% (209/246) in the FMR group [4]. The percentage of patients with MR severity grade ≤2 at 12 months post-procedure and the percentage of patients with New York Heart Association (NYHA) class ≤II at 12 months post-procedure were significantly increased as compared with the baseline in both the DMR and FMR groups (Fig. 2) [4]. Furthermore, the rates of hospitalization for heart failure were significantly decreased from 12 months pre-enrollment to 12 months post-discharge in both groups (Fig. 2) [4,6].

Major adverse events were defined as combined clinical endpoint of death, myocardial infarction, re-operation for failed surgery, non-elective cardiovascular surgery, stroke, renal failure, deep wound infection, ventilation, gastrointestinal complication,

	DMR (105 patients)	FMR (246 patients)
Procedural success	79% (83/105)	85% (209/246)
The rates of MR severity ≤ 2+ Beseline → 12 months	8.8% (9/102) → 85.3% (58/68)	15.7% (37/235)→ 82.8% (130/157)
The rates of NYHA ≤ II Beseline → 12 months	18.1% (19/105)→ 87.3% (62/71)	13.8% (32/246)→ 81.0% (132/163)
The rates of hospitalization for heart failure (per patient-year) 12-month pre-enrollment → post-discharge through 12-month	0.68 → 0.18	0.81 → 0.39

Fig. 2. Mitraclip efficacy in the integrated high risk cohort. In the Integrated High Risk Cohort, the procedural success rate was 79.0% (83/105) in the degenerative mitral regurgitation (DMR) group, and 85.0% (209/246) in the functional mitral regurgitation (FMR) group. The percentage of patients with mitral regurgitation severity grade ≤2 at 12 months post-operation was significantly increased as compared with the baseline in both the DMR and FMR groups [DMR, baseline 8.8% (9/102), 12 months 85.3% (58/68)] [FMR, baseline 15.7% (37/235), 12 months 82.8% (130/157)]. Also, the percentage of patients with New York Heart Association (NYHA) class ≤II at 12 months post-operation was significantly increased as compared with the baseline in both the DMR and the FMR groups [DMR, baseline 18.1% (19/105), 12 months 87.3% (62/71); FMR, baseline 13.8% (34/246), 12 months 81.0% (132/163)]. Furthermore, the rates of hospitalization for heart failure were significantly decreased from 12-month pre-enrollment to 12 months post-discharge in both the DMR and the FMR group (DMR, 0.68 → 0.18, FMR, 0.81 → 0.39).

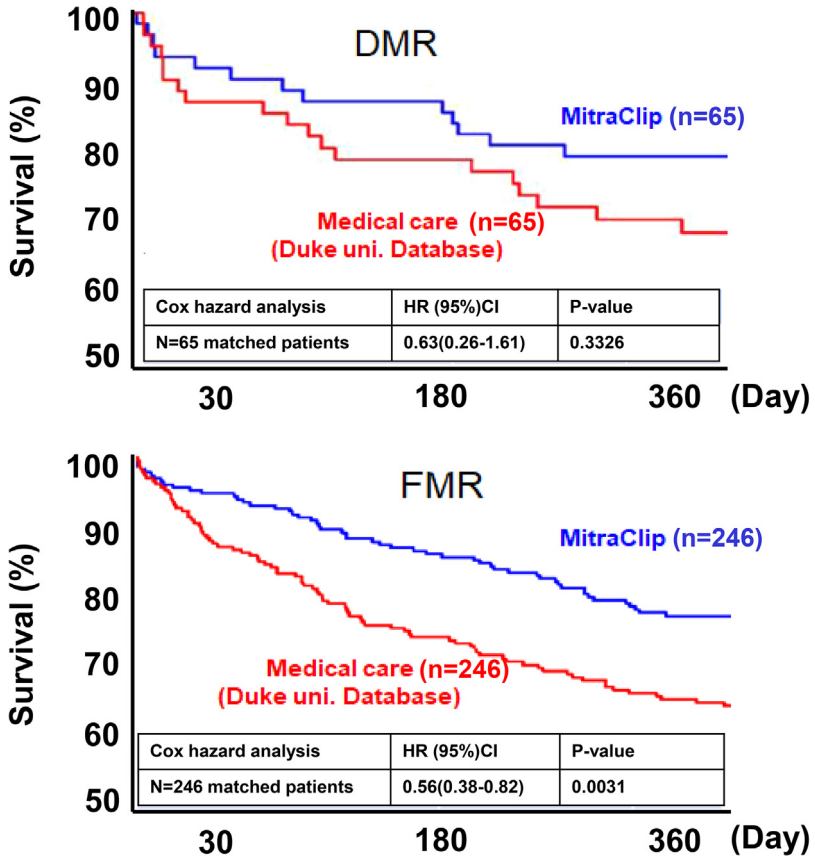

Fig. 3. Propensity score-matching analysis for mortality between the Integrated High-Risk Cohort and patients with medical treatment from Duke University database. The mortality rates at 12 months in the MitraClip group and the medical treatment group in Duke University database are 20.0% and 30.6% in degenerative mitral regurgitation (DMR) patients and 21.9% and 34.3% in functional mitral regurgitation (FMR) patients, respectively. These analyses indicated that transcatheter mitral valve repair using MitraClip did not increase the risk of mortality as compared with medical therapy in high-risk mitral regurgitation patients.

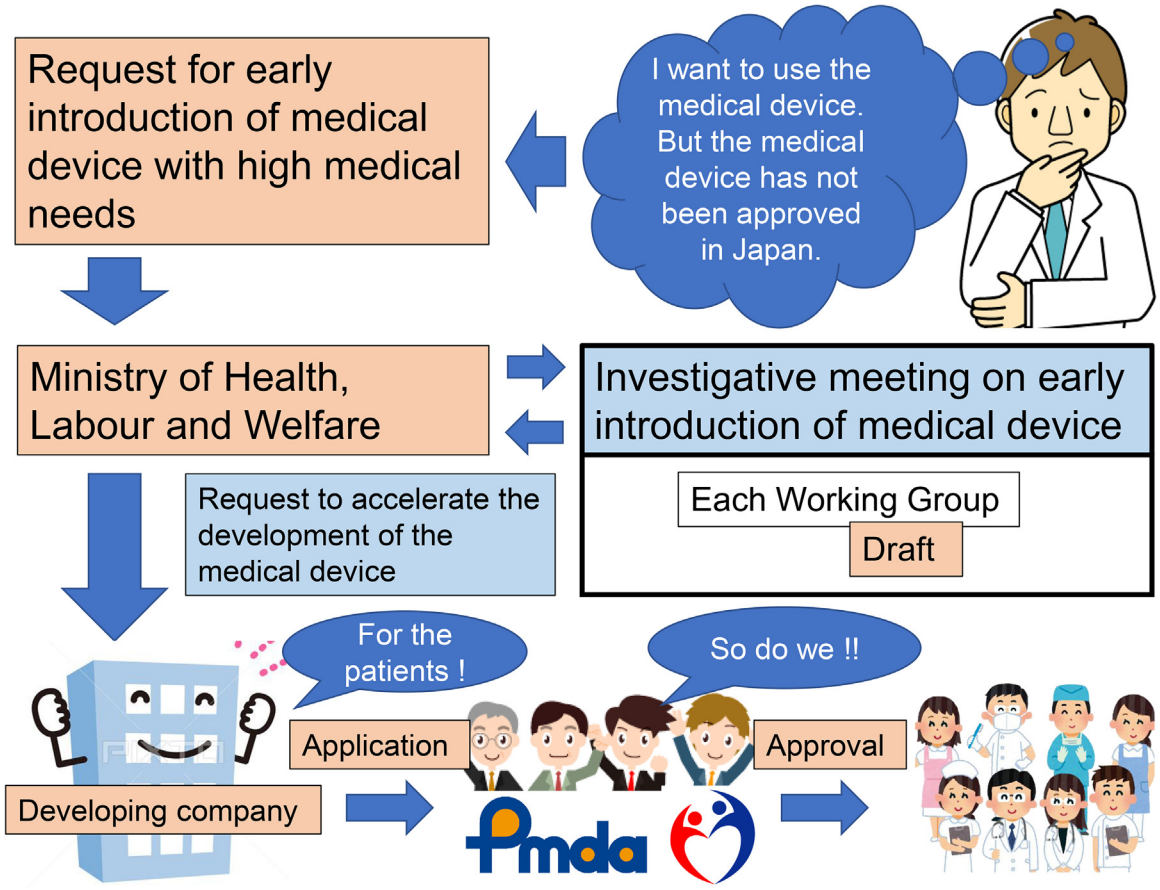

Fig. 4. Investigative meeting on early introduction of medical devices with high medical need. If an academic society or a patient group wishes to have access to a medical device with high need that has not been approved in Japan, but may have been approved in another country (although this is not necessary), a request for early introduction of the medical device can be submitted to the Ministry of Health, Labour and Welfare (MHLW). The draft request is evaluated in an investigative meeting on early introduction of the medical device after discussions in a working group. If the investigative meeting approves early introduction of the medical device, MHLW requests the developing company to accelerate the development of the medical device according to the chart. If a suitable company does not exist in Japan, MHLW publicly seeks a developing company.

new onset of permanent atrial fibrillation, septicemia, and blood transfusion. The major adverse event rates were almost the same in the DMR group and the FMR group (DMR: 36.2%, FMR: 38.2%) [4]. However, we could not judge whether these values were higher or not as compared with medical treatment. Therefore, we decided to use the Duke University database for informative data, and carried out propensity score-matching analysis to compare mortality with that in the Integrated High Risk Cohort. This analysis indicated that the transcatheter mitral valve repair using MitraClip [7] did not increase the risk of mortality in high-risk MR patients for mitral valve surgery (Fig. 3) [4].

In the Japanese domestic trial [8], the acute procedural success rate was 85.7% (12/14) in the DMR arm and 87.5% (14/16) in the FMR arm. There were no major adverse events at 30 days in either of the arms [4].

Basis of regulatory approval of the indication for FMR in Japan

The major findings from the two clinical data sets are as follows: (1) there were significant clinical improvements in NYHA class and hospitalizations for heart failure due to reduction of MR grade without adversely affecting long-term prognosis for FMR as well as DMR in the Integrated High Risk Cohort. (2) The Japanese domestic trial showed favorable results with the MitraClip in both DMR and FMR patients.

We had detailed discussions with academia and the Ministry of Health, Labour and Welfare on whether to conduct an additional randomized clinical trial for FMR, which the US Food and Drug Administration required, or whether to give approval for the indication of FMR without an additional trial. As DMR is a disease of the mitral valve itself, the clinical implication of improvement in MR is clear in patients with DMR. However, FMR is caused not by the mitral valve itself, but by left atrium or left ventricle dilatation due to ischemic heart disease or cardiomyopathy. Therefore, as improvement in MR is not a fundamental remedy for FMR, the clinical implication of improvement in MR remains unclear in patients with FMR.

Nevertheless, the Japanese Circulation Society guideline recommends surgical repair to both FMR and DMR (class 1 recommendation) if the left ventricular ejection fraction (EF) is more than 30%, whereas in the US guideline, surgical treatment for FMR is a class 2b recommendation and that for DMR is a class 1 recommendation [9–11]. In other words, it is considered in Japan that improvement in MR mechanically is clinically important in both DMR and FMR, in patients without severe left ventricular dysfunction. Furthermore, it has been reported that severity of MR correlates with poor prognosis [12]. This result might imply that improvement in MR mechanically could have some benefit even to FMR patients. Moreover, the medical need is very high, as there has been no effective treatment option for FMR patients at prohibitive risk for mitral valve surgery, who are resistant to medical therapy. Therefore, the Japanese Circulation Society submitted a formal request for early approval of the MitraClip for both DMR and FMR to the Japanese government. Another consideration was that

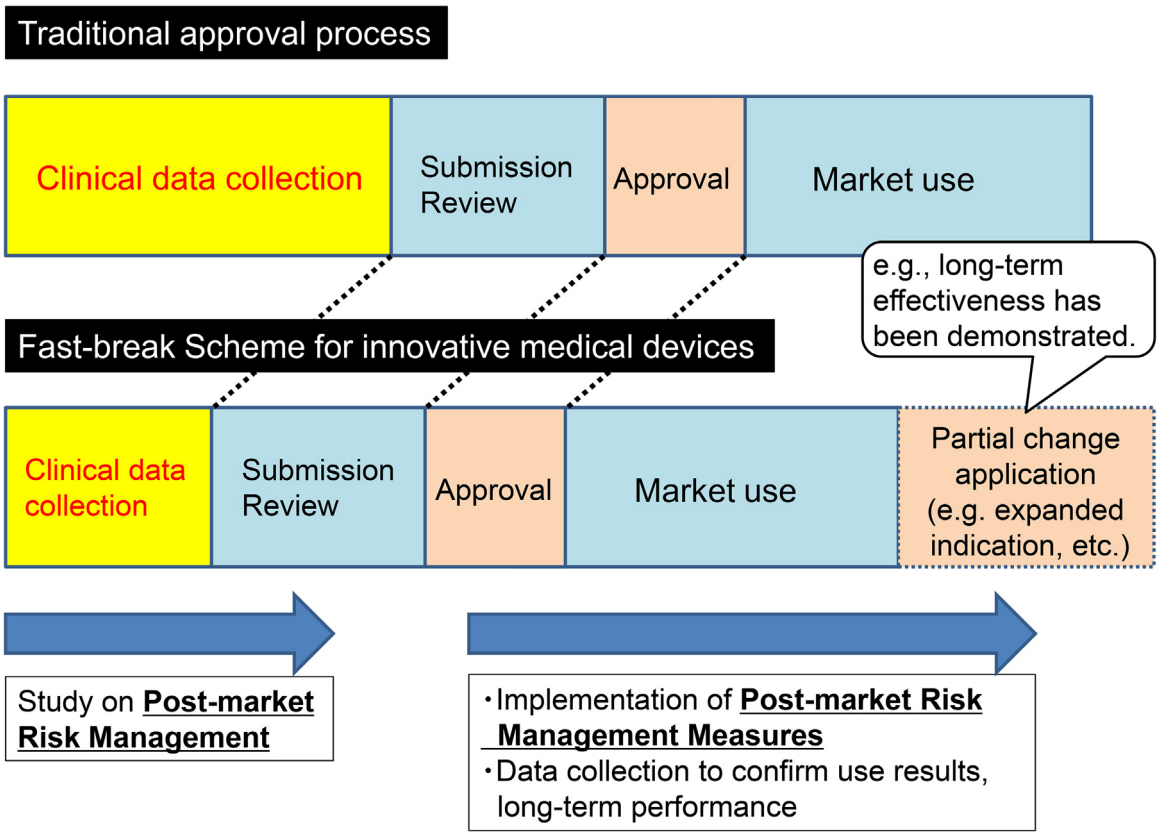

Fig. 5. Fast-break scheme for innovative medical devices. Under the traditional approval process, long-term data collection is needed. However, under the fast-break scheme, innovative medical devices satisfying all the prescribed criteria are approved based on existing data, conditional upon Use-Results Survey, leading to shorter data collection times than in the case of the traditional approval process. However, the scheme is to be applied only to those brand-new medical devices satisfying the following criteria: (1) no appropriate alternative medical devices, or a reasonable likelihood of higher efficacy and safety compared to existing products; (2) the target patient population is affected by life-threatening disease or serious disability in a daily life; (3) some supporting clinical evidence is available; (4) post-marketing commitment to an appropriate risk management plan in collaboration with relevant academic medical societies (e.g. sales restriction to certified experts and institutions) and rigorous real-world evidence collection and evaluation; (5) justification of difficulty to conduct a new prospective clinical trial.

Japanese universal care does not necessarily cover all the cost of a series of procedures or surgery in the case of off-label use of medical devices, although some insurance companies in the USA may do so. To accelerate patients' access to new medical devices in Japan, we have to decide on appropriate target patients of the medical device in terms of high medical need based on a risk–benefit balance evaluation.

On the basis of all these considerations, the MitraClip was approved for indications of both DMR and FMR in patients with preserved cardiac function at prohibitive risk for mitral valve surgery conditional upon a Use-Results Survey [13] that requires continuous enrollment of all MitraClip treated patients up to 500.

The recent Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MitraFR) study (n = 304 subjects) revealed that the frequencies of death or unplanned hospitalization for heart failure at 1 year were not significantly different between patients with percutaneous mitral-valve repair in addition to receiving medical therapy and those with medical therapy alone, among severe FMR patients [14]. However, another recent study, the COAPT trial (n = 614 subjects) showed that addition of MitraClip to maximally tolerated guideline-directed medical therapy resulted in a lower rate of hospitalization for heart failure and lower all-cause mortality within 24 months of follow-up than guideline-directed medical therapy alone, in patients with symptomatic heart failure and moderate-to-severe or severe FMR [15].

Following the approval of MitraClip in Japan, a Use-Results Survey [13] of up to 500 patents is ongoing to evaluate the efficacy and safety of the MitraClip in medication-resistant patients with symptomatic heart failure and severe DMR and FMR with maintained cardiac function, in order to obtain real-world data.

Future prospects to accelerate the development of innovative medical devices related to heart failure

Few medical devices or drugs related to heart failure have been introduced over the past 15 years in Japan [16,17]. To promote research and development in this area, the Ministry of Health, Labour and Welfare issued guidelines in 2011 on the clinical evaluation of drugs for the treatment of heart failure. This guideline indicates that not only benefits in mortality or morbidity, but also those in quality of life (QOL), including exercise tolerance and hospitalization for heart failure, would be acceptable for regulatory approval in Japan, when there is no appropriate alternative treatment without adversely affecting long-term prognosis [18].

Therefore, in our regulatory review of MitraClip, we evaluated the risk–benefit balance taking account of QOL, including improvement of NYHA class, and hospitalizations for heart failure without adversely affecting long-term prognosis, by using the Duke University database as informative data, and carried out propensity score-matching analysis to compare mortality with that in the Integrated High Risk Cohort.

However, as QOL is a subjective parameter, we were concerned about the possibility of bias. Recent studies revealed that results obtained with the Kansas City Cardiomyopathy Questionnaire

(KCCQ), a questionnaire based on subjective factors, had a strong correlation with clinical events [19,20]. Thus, it might be possible to reduce the burden of clinical trials by using adequate and well-established surrogate endpoints in the future. To establish an adequate surrogate endpoint, it will be necessary to collect data on both a hard endpoint and surrogate endpoint in a clinical trial, and to establish a good correlation consistently between them.

The Japanese government has initiated several policies to expedite patient access to medical devices by overcoming device lag. Examples include the investigative meeting on early introduction of medical devices with high medical need (Fig. 4) [22] and the "fast-break scheme" for innovative medical devices, taking account of the pre- and post-marketing balance of medical devices regulations in a product life cycle (Fig. 5) [1]. Well-established surrogate endpoints and these schemes would accelerate the development and introduction of medical devices related to heart failure. This would provide greater benefits to patients who require access to new medical devices, as well as to the companies developing them, via improved transparency and predictability of the medical device life cycle.

Conflicts of interest

The authors have no conflicts of interest to declare.

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