REGULATORY APPROVAL OF INNOVATIVE MEDICAL DEVICES: A CROSS SECTIONAL STUDY

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Author contributions:

HJM and CJP were involved in the study conception, acquisition of data, analysis of data, and drafting the manuscript. AHH, and APM were involved in the study conception, acquisition of data, analysis of data, and critical revision of the manuscript. DN, GZY and AD were involved in the study conception and critical revision of the manuscript.

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ABSTRACT

Objective: To investigate the regulatory approval of innovative medical devices.

Design: Cross sectional study of innovative medical devices reported in the biomedical literature.

Data sources: The PubMed database was searched to identify first-in-human studies of innovative medical devices. We searched between the 1st January 2000 and 31st December 2004 to allow time for regulatory approval.

Eligibility criteria for selecting studies: Articles were included if they reported a first-in-human study of a new medical device according to the FDA definition.

Main outcome measures: For each first-in-human study we determined the type of device, target specialty, involvement of academia, and involvement of industry. The FDA medical databases were then searched for approvals relevant to the device. The proportion of devices receiving regulatory approval was then compared using the Chi-square test.

Results: 5,574 titles and abstracts were screened, 493 full-text articles assessed for eligibility, and 218 first-in-human studies of innovative medical devices included. In all, 99/218 (45.4%) of the devices described in first-in-human studies ultimately received regulatory approval. Approvals included 510(k) clearance for devices determined to be substantially equivalent to another legally marketed device (78/218; 35.8%), premarket approval (PMA) for high-risk devices (17/218; 7.8%), and others (4/218; 1.8%). Devices were more likely to be approved if developed by industry alone compared to academia alone (57.9% vs. 10.9%; $p < 0.001$), or by both industry and academia compared to academia alone (40.6% vs. 10.9%; $p = 0.003$).

Conclusions: We identified a multitude of innovative medical devices in first-in-human studies, almost half of which received regulatory approval. The 510(k) pathway was most commonly used, and approval often preceded the published first-in-human study. For devices developed in academia, collaboration with industry was more likely to result in approval.

WHAT THIS PAPER ADDS

What is already known about the subject:

- Very few new drugs ultimately receive regulatory approval, but industry collaboration is a strong predictor of success
- Innovative medical devices have a distinct and historically less stringent approval pathway

What this study adds:

- Almost half of the innovative medical devices described in the literature ultimately receive regulatory approval
- The 510(k) pathway is most commonly used, and approval often precedes publication of a first-in-human study
- For devices, as with drugs, collaboration with industry is significantly more likely to yield approval

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INTRODUCTION

The introduction of innovative medical devices is fundamental to the advancement of healthcare. Historically, such innovations have been adopted with little scientific evidence to support their use.[1] Although many have greatly improved clinical outcomes, not all innovations are beneficial and some may be harmful. To this end, most jurisdictions have developed regulatory bodies such as the Food and Drug Administration (FDA) that report on the safety and effectiveness of innovations.[2]

In contrast to device development, the process by which new drugs find their way from bench-to-bedside is well established: (1) the development of the drug resulting in a first-in-human study, (2) the evaluation of the device in clinical trials, culminating in a regulatory approval for use, and (3) the adoption of the drug by physicians.[3] These translational barriers make drug development difficult.[2] In a study on the translation of highly promising basic science research, only 5% ultimately received regulatory approval.[4] Industry collaboration was found to be the strongest predictor of successful translation.

Device development generally proceeds through stages similar to those for drug development, albeit with some important differences.[2] Over the last few years, substantial progress has been made in the science of device innovation, particularly in surgery. The Balliol Collaboration has proposed the IDEAL model for safe surgical innovation, the central tenet being that innovation and evaluation can and should proceed together in an ordered and logical manner.[2 5-9] The role of regulatory approval in this process remains unclear, though bodies such as the FDA have repeatedly come under scrutiny in the past two decades.[10] Industry has previously been suggested as an important source of device innovation, and may more easily navigate the regulatory approval pathway. However, a recent study failed to demonstrate any significant association between industry collaboration and the translation of innovative devices.[11]

The aim of this study was to investigate the regulatory approval of innovative medical devices, and the relative contributions of academia and industry in this process.

METHODS

We performed a cross sectional study of innovative medical devices reported in the literature. We defined a medical device according to the US Food and Drug Administration (FDA) as an "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article..." We considered a device as innovative if there was no evidence of previous clinical study in the literature.

For each article reporting a first-in-human study of an innovative medical device, we defined academia and industry as involved with the development of the device if a relationship was described in the article. We considered a device as having regulatory approval if an entry could be found on the FDA medical device databases.

Search strategy:

The PubMed database (NCBI, Maryland, USA) was searched using the Boolean term: (device OR instrument OR apparatus OR implant OR "in vitro reagent" OR system) AND ("first in man" OR "first in human" OR "first experience" OR "first clinical" OR "early clinical" OR "early experience" OR "early human" OR "initial experience" OR "initial clinical" OR "initial human" OR "preliminary clinical" OR "preliminary experience" OR "preliminary human" OR "Phase 1" OR "Phase I"). This search term was selected on the basis of efficiency and being able to identify the most relevant studies. We searched between the 1st January 2000 and 31st December 2004 to allow time for regulatory approval as previous studies have reported a long translational lag.[4 12]

We included articles that reported a first-in-human study of an innovative medical device. We excluded articles if they only reported a preclinical study of a device because very few such devices are ultimately translated.[11] We also excluded articles if they reported on the novel use of an existing device, as we expected that most such devices would already have received regulatory approval.

We estimated based on a pilot study (between 1st January 2000 and 31st July 2000) that this search strategy would select sufficient articles to allow for meaningful analysis.

Titles and abstracts were initially screened to identify relevant articles (HJM and CJP, checked by AHH and APM). Full articles were subsequently obtained and further assessed for eligibility. In each instance, we reviewed the reference list and searched the PubMed database using the device name to ensure that we did not miss a related previous clinical study (that would result in their exclusion). Discrepancies were resolved by consensus.

Medical devices:

For each first-in-human study of an innovative medical device we determined the type of device, the target specialty, the involvement of academia, and the involvement of industry (HJM and CJP, checked by AHH and APM). The types of device were based on the FDA definition and the target specialties were drawn from the FDA databases. We considered academia and industry to be involved in the development of a device if a relationship was described in the author affiliations, main text, or acknowledgements of the article. Discrepancies were resolved by consensus.

Regulatory approvals:

For each innovative medical device we searched the FDA databases for a relevant regulatory approval. The FDA recognises several types of regulatory approval pathway depending on how novel the device is, including: premarket notification [510(k)] if the device is "substantially equivalent" to a predicate device; premarket approval (PMA) if the device is "not substantially equivalent", and requires reasonable evidence of safety and effectiveness; and others such as humanitarian device exemption (HDE) if the device is for use in patients with rare diseases or conditions. We searched the FDA 510k, PMA, and HDE databases using the device name, applicant name, and relevant keywords (HJM and CJP, checked by AHH and APM). All the searches were performed in August 2015, allowing a minimum of 10 years from publication to regulatory approval. Discrepancies were resolved by consensus.

Statistical analysis:

We used the Chi-square test to compare differences in regulatory approval between the following groups: devices developed by industry alone versus academia alone; devices developed by both industry and academia versus academia alone; and devices developed by both industry and academia versus industry alone. First, we compared the proportion of devices receiving any regulatory approval (versus no approval). Second, we compared the proportion of devices receiving 510k approval (versus any other approval). We considered differences to be statistically significant if P was less than 0.05. All statistical analyses were performed using SPSS 22.0 (IBM, New York, USA).

RESULTS

Search strategy:

In all, 5,574 titles and abstracts were screened, 493 full-text articles assessed for eligibility, and 218 first-in-human studies of innovative medical devices included (Figure 1). These articles were published in 135 different journals, including Catheter (12/218; 5.5%), Surgical Endoscopy (7/218; 3.2%), and Annals of Thoracic Surgery (6/218; 2.8%). The corresponding authors originated from 28 countries, but the majority were located in the USA (70/218; 32.1%) and Germany (43/218; 19.7%).

Medical devices:

Most of the medical devices reported were instruments (86/218; 39.4%) or implants (79/218; 36.2%) (Table 1). Devices were developed by industry alone (140/218; 64.2%), academia alone (46/218; 21.1%), or both (32/218; 14.7%).

Regulatory approvals:

Of the 218 devices described in first-in-human studies, 99 (45.4%) ultimately received regulatory approval (Table 2). Approvals included 510(k) (78/218; 35.8%), PMA, (17/218; 7.8%), and HDA (4/218; 1.8%). The median lag between publication of the first-in-human study and regulatory approval was 2 months (interquartile range -10.8 months to 26.3 months); 43 devices (43/218; 19.7%) were approved before a first-in-human study was published.

Statistical analysis:

Devices were more likely to be translated if developed by industry alone compared to academia alone (57.9% vs. 10.9%; p <0.001), or by both industry and academia compared to academia alone (40.6% vs. 10.9%; p = 0.003). There was no significant difference in translation between devices developed by industry alone compared to both industry and academia (57.9% vs. 40.6%; p = 0.114).

There was no significant difference in the proportion of 510(k) and other approvals that were awarded to industry alone, industry and academia, or academia alone (p >0.1 in all cases).

DISCUSSION

Principle findings:

We identified a multitude of innovative medical devices in first-in-human studies, almost half of which received regulatory approval. The 510(k) pathway was most commonly used, and devices often received regulatory approval before a first-in-human study was published.

The 510(k) pathway is a fast-track system that allows the regulatory approval of a device that is "substantially equivalent" to a predicate device. A device is considered substantially equivalent if: (1) it has the same intended use as the predicate device and (2) it has the same technological characteristics or, if it has different technological characteristics, information is provided that demonstrates that it is at least as safe and effective as the predicate device. Clinical studies are therefore not usually required.

The introduction of a device after it has been approved through the 510(k) pathway is usually unregulated, unstructured and variable.[2] A device may be introduced in the form of a research study but, more frequently, may be published as a non-comparative trial without special institutional board review. Although many such devices are safe and effective, the dangers of this process are obvious and have been reported.[10] The Balliol Collaboration has proposed the IDEAL model for safe innovation to address this shortfall. [2 5-9] Moreover, the FDA has recognised the need for reform and has announced a new vision for post market surveillance of new devices.[13]

Industry was found to have a role in the development and translation of the majority of devices identified. For devices developed in academia collaboration with industry was associated with

greater translation. Interestingly, the proportion of 510(k), PMA and other approvals that were awarded to industry and academia were comparable, suggesting that the greater translation of devices developed by industry did not simply reflect a propensity for less disruptive and lower risk innovations. This finding supports efforts such as the Medical Device Innovation Consortium (MDIC) that facilitate collaboration among academia and industry in order to foster technology transfer.[14]

Comparison with other studies:

Contopoulos-Ioannidis et al evaluated the translation of promising basic science research but focused on drug innovation[4]. Of 101 innovations, 27 resulted in at least one randomised trial, and only 5 received regulatory approval. We speculate that this is because drug innovation has a distinct and historically more stringent regulatory approval pathway than device innovation; crucially, new drugs must be proven to be safe and effective in clinical trials before their approval.[2 15].

In a previous study we investigated the translation of innovative devices from the laboratory to first-in-human studies[11]. In contrast to the present study we found that clinical rather than industry collaboration was the most important predictor of translation; devices developed with clinical collaboration were over six times more likely to lead to a first-in-human study than those without. It is likely that this incongruity is the result of the varying role of clinical and industry collaboration through the continuum of translation; early translation may be more reliant on clinicians to drive early clinical studies, and later translation more reliant on industry to navigate the regulatory approval pathway.

Limitations:

We recognise several limitations to this study. We determined whether a device had regulatory approval using only the FDA medical device databases. The proportion of medical devices receiving regulatory approval was therefore undoubtedly an underestimate. The reason for selecting the FDA, rather than other licensing authorities, was because the USA represents the largest medical device market in the world, and the FDA provides public databases and search engines that allowed for a systematic search strategy.

We restricted our analysis to first-in-human studies of innovative medical devices reported in the biomedical literature. This may have favoured more novel devices, which clinicians might have thought warranted publication in a peer-reviewed journal. The proportion of devices approved through the 510(k) pathway was therefore also likely to be an underestimate.

Conclusions:

The optimal framework for the regulatory approval of medical innovations remains unclear. The pathway by which new drugs find their way to translation is rigorous, but may stifle innovation.[2 4] Conversely, this study suggests that many new devices do receive regulatory approval, but often lack clinical trial data supporting their safety and effectiveness.

The IDEAL model makes several proposals for the staged introduction of innovations in surgery (and other disciplines that offer complex interventions), including randomised controlled trials to assess safety and effectiveness.[2 5-9] At present, few relevant randomised controlled trials are published, and fewer still meet current quality standards for optimal reporting.[16 17] Changes in the regulatory approval of devices that would require trials for proof of safety and effectiveness might promote adherence to the IDEAL model.[6]

Although clinical trials are often not required for the approval of new devices, the regulatory pathway is still complex and costly. This study has found that for devices developed in academia, as with drugs, collaboration with industry is significantly more likely to yield approval.[4] Policies that encourage interactions between academia and industry can therefore be expected to enhance translation.

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TABLES

Table 1. Characteristics of innovative medical devices, and whether they ultimately received regulatory approval for use.

	Total (n = 218)	**Approval (n = 99)**
Type of device		
Imaging	31	11
Implant	79	37
Instrument	86	47
Laboratory analysis	3	1
Monitor	10	3
Physical therapy	7	0
Other	2	0
Target specialty		
Anesthesiology	5	2
Cardiovascular	67	40
Clinical Chemistry	2	0
Clinical Toxicology	1	0
Dental	2	0
Ear, Nose and Throat	12	3
Gastroenterology and Urology	19	7
General and Plastic Surgery	22	11

General Hospital	8	2
Hematology	2	1
Neurology	15	6
Obstetrics and Gynaecology	11	6
Ophthalmic	11	5
Orthopaedic	22	10
Physical Medicine	6	0
Radiology	13	6

Table 2. Development of innovative medical devices, and whether they ultimately received regulatory approval for use.

	Total (n = 218)	**Approval (n = 99)**	**510k (n = 78)**	**PMA (n = 17)**	**HDA (n = 4)**
Academia alone	46	5	5	0	0
Academia and Industry	32	13	10	1	2
Industry alone	140	81	63	16	2

FIGURES

Figure 1. Flow chart demonstrating the selection of first-in-human studies of innovative medical devices.