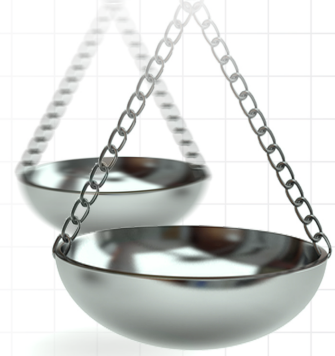
Editorial





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# A long adolescence: when will medical apps come of age?

"Once developers can prove that their apps are effective, they will then need to prove that they are safe and reliable."

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Medical and popular media are replete with articles highlighting the latest innovation in medical apps. Despite this positive press and strong interest from patients and clinicians, medical apps are being priced at a significant discount to the conventional therapies they aim to augment or replace. Indeed a recent survey found that 41% of adults would not pay for health-related apps and 43% would expect to pay less than US$6 for an app [1]. Although some apps are produced and distributed by charities and not-for-profit organizations, most apps on the market are commercial products. For these commercial developers, a clear goal is to create a product that has a significant clinical effect comparable to a conventional therapy and then to be able to market that product at an equivalent price point.

Out of the 165,000 health-related apps currently available for download [2] very few retail at significant price points, let alone parity with equivalent conventional therapies such as pharmaceuticals. Exceptions include Astra Zeneca's cardiac rehabilitation app Connections for Cardiac Health (US$45/month or US$249/year) [3] and WellDoc's Blue Star diabetes app (c. US$100/month) [4]. Why are these apps the exception and what is stopping these products achieving price parity with conventional therapies?

## Evidence base

Proven clinical effectiveness is essential for apps to justify a high price point in an competitive healthcare environment. Unfortunately for app developers, several recent meta-analyses have concluded that there is not currently an evidence base to support the widespread use of medical apps [5]. Indeed, by contrast to the overwhelmingly positive popular media, the scientific literature is quite critical about the majority of apps available for download.

Currently, the two largest segments of the medical app market are mental health and diabetes, comprising 29 and 15% of the market, respectively [6]. A recent review of mental health apps concluded that there was a complete lack of experimental evidence for hundreds of available apps [7]. Similarly a systematic assessment of insulin dose calculating apps in the UK [8] showed that whilst physicians and patients were happy to use these apps, there was a dangerous lack of standardization and that potentially fatal errors were possible. The authors concluded that physicians exercise substantial caution and actually warn patients about the risks of some apps.

These concerns and criticism of the current app market send a strong signal to physicians and commissioners of health services that they need to exercise some caution when recommending apps for patient use. In this environment it may be challenging for app developers to attain high price points for their apps, even if their product is high quality and suitably evidenced.

It is likely no co-incidence that the apps that command the highest price point in the

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market are those with the most robust evidence base. However, compared with conventional interventions the evidence base for even the best apps is scant by comparison. This situation will change rapidly over the next few years as a portion of the US$4.5 billion invested in digital healthcare in 2015 [9] is likely to be focused on developing the evidence base and expanding the publication of high-quality evidence. On the back of this research it is likely there will be a growing price difference between poorly evidenced low-quality apps and a much smaller number of high-quality clinically evidenced apps.

High-quality comparative effectiveness research will be an important tool for app developers looking to make a case for pricing parity with conventional therapies. How those research trials should be conducted remains an open question.

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Although one could in theory 'blind' a research trial looking at two different apps, for example by removing branding information, or altering an underlying algorithm it is impossible to 'blind' a comparison between an app and say a pharmaceutical agent. The app arm of the trial will always be aware they are using an app! This could lead to biases both positive and negative depending on the patient demographics and attitudes, making head to head comparisons methodologically challenging. Despite these challenges, head to head trials of apps against conventional therapies are essential for app developers to make the case for their products being used in place of and priced equal to these conventional therapies.

Even if a convincing evidence base showing clinical parity with conventional therapies is developed over the next few years, this may not be enough by itself to enable price parity. There are still multiple barriers for even high quality apps to overcome before they become mainstream medical therapies with the concomitant price point. One of the most pressing issues facing app developers is the uncertainties surrounding regulation.

## Regulatory environment

The US FDA currently classifies medical apps as medical devices and has recently produced updated guidance [10] concerning their approval and marketing. Within this updated guidance, the FDA recognizes three categories of apps using a 'risk-based' approach. The majority of apps according to the FDA are either clearly not medical devices, or are potentially medical devices but with a low risk of harm to patients. The FDA will not currently regulate these low-risk apps directly but exercises 'enforcement discretion'. This means the apps may come under scrutiny in the future if there are concerns expressed or new evidence emerges. Examples of apps for which the FDA exercises 'enforcement discretion' include those which track personal health data, medicine compliance or provide access to health records.

The third category of apps the FDA recognizes are those which can be classified as medical devices and due to their high risk of injury to patients need full regulation. An example of these apps are those that connect to and potentially control existing devices such as insulin pumps or fetal monitoring systems. Also included are apps that analyze cardiac rhythms or help diabetics calculate insulin dosages. These apps must have full FDA oversight and approval prior to marketing.

In the US there has been backlash from app developers and proponents of IT in healthcare who claim that the ambiguity caused by 'enforcement discretion' discourages innovation and adoption of apps [11]. The system operating in Europe is not necessarily preferable. The European Medical Device Directive recognizes that some software classifies as a medical device requiring a Conformité Européenne watermark prior to use. Although this includes commonly used apps which function as dosage calculators and other point of care tools [12] many such apps available in the UK do not carry a Conformité Européenne mark and are not registered with the Medicines and Healthcare Products Regulations Agency.

This evolving and confusing regulatory environment is causing great uncertainty for app developers, patients and physicians alike. Research funded by the UK Technology Strategy Board [13] has highlighted the complex and uncertain regulatory environment as a key barrier for wider uptake of medical apps. These opinions were found in multiple groups including the commissioners of medical services in the UK. This uncertainty for the commissioners likely prevents app developers achieving pricing parity even for high-quality and evidenced apps. Although gaining regulatory approval from designated bodies can be time consuming and expensive, electively seeking regulatory approval may be preferable to the ambiguity that may otherwise be present.

However for physicians and commissioners of medical services an app with an FDA approval may not be a clear indicator of quality. Most apps currently approved by the FDA have done so through the 501(k) process, which does not require clinical trials and is thought to be the least stringent [14] of the FDA's approval pathways. For a 501(k) application, all that is required is for the developer to show their app is 'substantially equivalent' to a previously approved app or device. For physicians used to relying on FDA approval as a marker

of quality – as it clearly is with pharmaceuticals – the current system creates further confusion.

A further aspect of regulation that needs clarity is the point at which a medical app would need to be 'prescription only'. For pharmaceutical agents, a medicine can be sold 'over the counter' without prescription if the patient can easily self diagnose and monitor their condition, the agent is effective and has low toxicity without requiring any special monitoring regimen [15]. Although most medical apps are likely to fall into this category, there is no clear criteria for which apps should have 'prescription only' status.

## The path to parity

In the quest for price parity with conventional therapies, app developers first need to focus on the evidence base. Where apps are operating in areas with existing evidence and clinical guidance it is essential that apps comply with these. Development of a quality watermark to reassure patients, physicians and commissioners will increase confidence in complying apps. This type of quality assurance in a new market can be challenging – the National Health Service Health Apps Library was piloted in 2013 but closed after 2 years when researchers showed that two-thirds of the apps in the library put patients at risk by transmitting unencrypted information over the internet [16]. The National Information Board is in the process of developing new standards, but these will not be ready until 2018 [17]. In addition, the private sector also has efforts underway to develop a quality mark for apps but currently there is no widely agreed and reliable quality standard. Once a quality mark becomes mainstream and accepted, it will bolster the case for app developers that their products are of high quality, reliable and safe.

For apps that are offering a completely new medical product, conforming to existing evidence and guidance is unlikely to be sufficient. For example, collaboration between IBM Watson and Medtronic aims to create an artificial intelligence app that can predict blood sugar levels 3 h in advance [18]. Because of this app's novelty, it's unlikely to have any existing guidelines or evidence base to measure it against. For completely novel apps such as these it is essential that app developers conduct their own clinical trials to support their products in a similar manner to a new pharmaceutical agent. Companies such as WellDoc, which has marketed a novel diabetes app, have released data to support its use [19], but the data released to date are unlikely sufficient for robust head-to-head comparative effectiveness analysis.

Once developers can prove that their apps are effective, they will then need to prove that they are safe and reliable. Regulators such as the FDA and Medicines and Healthcare Products Regulations Agency should continue to clarify which apps they consider high and low risk as technology evolves. Once designated low risk, these agencies could remove themselves entirely from the regulatory process and instead support the development of the quality marks described above. This would enable regulators to concentrate solely on novel high-risk apps and subject them to rigorous review and testing.

With the twin pillars of quality and safety in place, the app market will come of age.

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