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Feature

Digital biomarkers for post-licensure safety monitoring

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Post-licensure safety data form the cornerstone of safety surveillance. However, such data have some limitations related to the subjectiveness of reporting and recording, primary purpose of the collected data, or heterogeneity. Routine capture of richer data would in part help mitigate these limitations, enabling earlier, more reliable safety insights. Digital health tools that remotely acquire health-related information are increasingly available and used by patients and the wider population. However, they are rarely used for pharmacovigilance purposes. Here, we review different cases that reveal the opportunities and challenges of using these technologies for enhanced safety assessment in routine healthcare delivery. We believe such approaches will advance our understanding of the safety of drugs and vaccines in the future.

Keywords: Digital health tools; Digital biomarkers; Safety; Pharmacovigilance

Introduction

Drug and vaccine candidates progress along the development continuum to approved use, and different data sources offer insights of varying importance throughout the product lifecycle.[1,2] Data captured during or after routine healthcare delivery play a crucial part in ensuring their appropriate and safe use.

Pre-approval human safety assessment is based on data from randomised clinical trials with some use of real world data (RWD) sources to contextualise experimental data, for example through natural history studies.[3] After approval, although RWD are used to conduct studies to evaluate specific issues or concerns with epidemiologic approaches, spontaneous adverse drug reaction reports remain the cornerstone of pharmacovigilance in terms of identifying potential emerging safety issues.[4,5] However, although spontaneous reports provide a sensitive and effective system for identifying suspicions of emerging safety issues, they have well-established limitations.[6] In particular, suspected safety outcomes need to be recognised and reported, and often only small amounts of supporting data are provided. Additionally, data usually just refer to a specific time point, although some time-constrained follow-up is at times provided. Spontaneous safety reports provide a precious insight into what healthcare providers are concerned[7]; but this strength is also a limitation because there can also be subjectivity in the process regarding when and how to report, as well as what information to impart. Safety adverse events (AE) are often reported in a binary fashion (occurred or not) and, although additional details can be provided in narrative, this is rarely valuable. Huge efforts are placed internationally into processing such reports and gleaning as much information as possible. Secondary use of RWD (electronic medical records, registries and insurance claims) is now common in

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pharmacovigilance but also suffers from limitations. Such data are often subjective, are primarily recorded for other purposes and their recency can be problematic.[4] Sometimes, prospective data collection is done specifically for safety outcome monitoring (e.g., registries); but this tends to also focus primarily on subjective data collection.[8]

Digital health tools (DHTs; see examples in Fig. 1) that remotely acquire health-related information from individuals are increasingly available and used by patients and the wider population. 'Digital biomarker' is a common term used to describe the data collected through DHTs, typically defined as: "An objective, quantifiable measure of physiology and/or behaviour used as an indicator of biological, pathological process or response to an exposure or an intervention that is derived from a digital measure".[9]

Digital biomarkers and traditional safety data sources have strengths that are complementary – the former being rich and continuous, the latter having a high degree of veracity. The combination of these data types has the potential to facilitate more robust safety monitoring systems.

Although digital biomarker data are currently commonly collected in drug development programmes for enhanced efficacy assessment,[10–12] there is for now little use of digital biomarkers for safety monitoring in routine healthcare delivery. The objective of this paper is to discuss how digital biomarkers might be used more broadly in routine healthcare delivery to enable the provision of more granular information to support safety evaluations. We describe several case studies where DHTs have been used in a variety of scenarios and highlight the key advantages that would benefit our current pharmacovigilance capability. We also discuss the current barriers to more widespread adoption for different safety needs and conclude with how we expect digital biomarkers and other emerging data streams will augment our approaches to support monitoring the safety of drugs and vaccines in the future.

Case studies

Case study 1: richer, timely AE data during drug or vaccine development

In drug and vaccine development programmes, clinical trial sponsors collect a vast amount of data from study participants, some of which is related to safety. These include (but are not limited to) vital signs, drug concentration in blood or reactogenicity. However, most of these data types are discrete measures taken infrequently during clinical examination and traditionally require patients to physically travel to a clinical site to perform the tests. A typical clinical trial has a limited number of scheduled visits where vital signs and physical examination data are collected; but any safety information in between visits relies on it being reported by the participants.

The emergence of digital technologies enabling objective, remote and continuous (or semi-continuous) study participant monitoring outside the clinical sites offers the potential to generate new insights that are not available through infrequent examination at clinical sites. As an example, Weiner *et al.* suggested that semi-continuous monitoring of vital signs (e.g., temperature, heart rate, blood pressure) in early-phase vaccine trials could allow identification of low-incidence safety events predictive of inflammation or reactogenicity, which can otherwise emerge during larger late-phase trials or after approval.[13] One hundred and forty three healthy participants were injected with one of six antiviral vaccines or placebo (20 or 21 participants per group). Their vital signs were monitored for 5 days

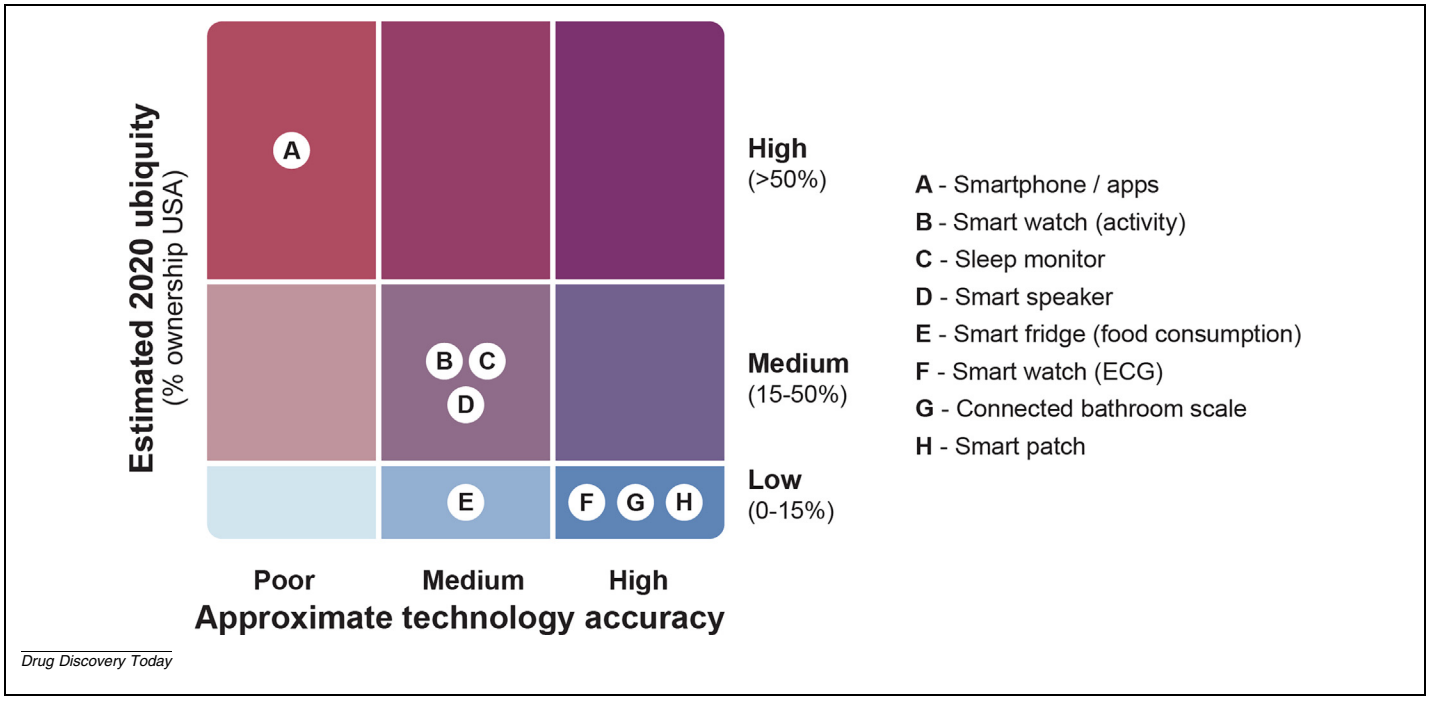

FIGURE 1

Examples of digital health tools potentially useful for safety evaluation and pharmacovigilance (non-exhaustive list). Abbreviation: ECG, electrocardiogram. Note that: (i) ubiquity of these technologies is growing rapidly year-on-year; (ii) accuracy (and reliability) strongly depends on the specific measure and on the device manufacturer. Ubiquity data were extracted from www.statista.com.[17]

immediately after vaccination (days 0–3 data recorded 4-hourly; days 4–5 data recorded 12-hourly). This resulted in > 20-times the amount of data that would have been collected in a traditional study design. One of the groups exhibited a transient rise in baseline temperature of 0.3 °C and a lack of expected decrease in mean heart rate in the first night (12–24 h post-vaccination). These subtle changes, which were assessed as representing an innate potent immune response, were still within the normal (safe) range but they would not have been detected in conventional trials if, at most, once-daily monitoring was performed, as has historically often been the case.[14] In this particular study, these measurements were taken using standard hospital equipment, resulting in supervised, high-quality and complete data. Nevertheless, novel remote monitoring sensors also enable capturing this information affordably and reliably, which can facilitate widespread data collection during vaccine or drug testing and post-approval. However, it is anticipated that, when deployed in the real-world, novel remote monitoring sensors will deliver large volumes of data that might be of lower quality and, hence, analysis and interpretation can be complex. Nevertheless, monitoring of digital biomarker data could provide an efficient approach that can complement the current approach focused on assessment of suspected AE reports arising from randomised clinical trials.[15,16]

Case study 2: consumer-grade wearable data for monitoring of atrial fibrillation

Globally, >400 million wearable devices were shipped in 2020.[17] These devices capture varying types of information related to the physical activity and physiology of users. They are currently mainly used by walkers, runners or people who simply want to track or improve their level of fitness, but increasingly by the wider population. Physical activity and pulse rate are the most common variables captured by these devices, from which other measures, such as sleep patterns, can be estimated.[18,19]

Physical activity patterns are typically derived from miniature inertial sensors, a well-established technology that has been available for many years. Optical sensors are routinely used to measure user pulse-rate using a technique named photoplethysmography. Individual measures of activity and pulse rate without contextualisation are unlikely to provide meaningful clinical information that can be attributed to a safety-related event. By contrast, continuous monitoring could enable the detection of potential cardiac issues that can be derived from drug usage (e.g., skipped beats, abnormally fast or slow heart rates without associated increase or decrease in activity intensity, arrhythmias, etc.). Algorithm development and validation is key to detect these abnormalities reliably.

Atrial fibrillation episodes are often not recognised and can lead to stroke.[20] A prospective clinical study evaluated whether a smartwatch was able to detect atrial fibrillation during regular use.[21] Over 419 000 US citizens were monitored for a median 117 days and received a notification if the wearable device detected an event of irregular pulse, in which case they were given the opportunity to wear an electrocardiogram patch to verify the cardiac event. The probability of a participant being notified of an irregular pulse was very low (0.52 %, ranging from 0.16 % of those aged 22–40 years to 3.1 % of those aged ≥ 65 years). However, from those participants that were sent notifications and had returned electrocardiogram patches with analysable data, 34 % indeed had atrial fibrillation. From those patients that did not receive a notification (and completed the end-of-study survey) only 1 % received a new (after-study) atrial fibrillation diagnosis, whereas 44 % of those that received a notification received a medical diagnosis within the following 90 days. Data quality and compliance with wearing the device was not specifically assessed but poor quality or compliance would have resulted in lower probability of detecting these events. Although further algorithm optimisation and validation are necessary (current algorithms resulted in > 50 % false positives), these data show the potential of a consumer-grade wearable device to detect heart-related events in the real world. This could offer important insights into safety-related events that arise from drug use, particularly when combined with electronic health record or AE reporting data.

Case study 3: Mobile app for diagnosis of skin conditions

Adverse cutaneous reactions such as skin rash, hives or blistering are common to many types of drugs. These reactions are in many cases undetected (if mild, patients might not report them) and misdiagnosed by non-specialist general practitioners and nurses,[22] leading to poor patient outcomes, such as delayed or inadequate treatment. More serious cutaneous AEs or events that lead to an unfavourable benefit:risk profile have led to restrictions in drug usage or even withdrawal.[23,24] Sparsity and lack of detail in collected data can also present a barrier to accurate diagnosis even by experts. This could also apply to more-serious skin reactions such as Stevens–Johnson syndrome.

Liu *et al*. developed a deep learning system to provide a differential diagnosis of skin conditions.[25] The system was trained using > 16 000 de-identified cases (including images and associated metadata such as demographic information and medical history) and validated using > 3700 cases, all from a tele-dermatology practice serving 17 different sites. The deep learning system was able to distinguish between 26 common dermatological conditions representing ~ 80 % of diagnoses seen in primary care. Its diagnosis accuracy was noninferior to six expert dermatologists and was superior to six general practitioners and six nurses.

The system was developed using existing clinical images and data from a single dermatology practice; but it could be applied to several other use-cases, including assisting clinicians in triaging cases or improving diagnosis accuracy of non-specialists (minimising referrals). Importantly, the tool can be integrated in a mobile phone app and be made available to the wider population and could help identify skin conditions based on images taken by patients using their phone's camera. Indeed, the mobile app has been awarded a Conformité Européenne (CE) mark for use as a medical tool (thus fulfilling Medical Device Regulations) in Europe, although it has not yet been given clearance in the USA.

Currently, owing to the accuracy of the algorithm, the system does not intend to replace human diagnosis but it is superior to patients searching for information

online. The algorithms were optimised to minimise false negatives in specific conditions such as skin cancer; but that is inevitably done at the expense of false positives, meaning that some patients might be advised to check something that will be shown to be benign.

A recent review of artificial intelligence systems being developed for diagnosis of skin conditions concluded that accuracy is typically lower in dark skin types owing to an imbalance in the training data (there are fewer images of dark skin types available for algorithm training).[26] Such a potential bias in the algorithm performance might result in inadequate monitoring of specific populations. However, over time, as the tool becomes more widespread, the accuracy of the algorithm has the potential to improve through an extended and better-balanced training dataset. Even if the diagnosis was to remain challenging at an individual level, incidences of adverse skin reactions, for example owing to drug intake, could still usefully be identified at population level.

Case study 4: Covariates not typically available in existing sources

New types of data captured through consumer devices could also enhance the detection of emerging safety issues, particularly those data types that are not typically reported in spontaneous reports or available in existing data sources (e.g., weight change, food consumption or speech patterns).

A systematic literature review by Leslie *et al*. on weight gain as an AE of some commonly prescribed drugs included data from 43 randomised studies (duration $\geq$ 3 months) involving > 25 000 participants who had been prescribed a drug considered obesogenic. The 'obesogenic' drug was compared with placebo, an alternative drug or other treatment.[27] Results provided evidence of weight gain for all drugs included, although differences in dosage, patient populations and diet advice provided to participants make generalisation of results difficult. This important AE of weight gain is often not recorded or is reported with insufficient detail, resulting in potentially seriously negative consequences for patients. The emergence of consumer-grade technologies for monitoring weight changes, such as connected bathroom scales, or eating patterns[28] could facilitate the detection of changes over time and do so in near-real time. This would lead to better identification of meaningful trends at population levels.

Speech impairment (stuttering) is another common AE typically underreported. Speech analysis is becoming a widespread tool in the monitoring of clinical conditions, particularly in neurodegeneration, showing promise in diagnosing disease and detecting subtle changes over time.[29,30] This can be done remotely through a mobile phone or other digital communication means. The mathematical models that were developed to interpret speech were tailored for this purpose; but similar methodologies can be deployed to identify those speech features that are indicative of safety concerns.

Other well-known adverse effects of many drugs include daytime sleepiness and night-time sleep disruption, which are typically reported by patients based on their own perception of sleep quality. Different novel digital technologies increasingly enable accurate quantification of sleep patterns in the real world.[31] Chinoy *et al*. evaluated the performance of seven consumer-grade (including four wearable) devices in tracking sleep, compared with polysomnography – the gold-standard sleep measure.[18] The study included 34 young healthy participants who used the consumer-grade devices over several nights and were monitored in a sleep clinic alongside polysomnography. Findings demonstrate that most of the consumer devices are promising in their initial validity against polysomnography, except in assessing specific sleep stages. However, additional validation is warranted, especially in other devices, populations and settings, to further define the strengths, weaknesses and limitations of using consumer-grade devices to assess sleep noninvasively in a real-world setting.

Discussion

Safety post-marketing surveillance of drugs and vaccines focuses primarily on spontaneous reports and analysis of RWD, including healthcare databases, registries and transactional insurance claims databases. The wider use of and potential ubiquity for digital biomarkers suggested by the examples presented above offer a glimpse into the added longitudinality, timeliness, richness, completeness and objectivity that could be possible, and therefore the ability to have more detailed and ultimately also more personalised view of safety. However, the greater objectivity, volume and heterogeneity of data systems and processes and consequent capture moving away from textual structured data will require reconsideration of analytics and process. More precisely, because pharmacovigilance needs to effectively highlight emerging safety issues, systems will need to be geared to best analyse digital biomarker data at large scale while maintaining high specificity. In addition, because the use of biomarker data needs additional resources, it must demonstrate superiority in at least some circumstances to augment or replace traditional approaches. To extract relevant safety information from digital biomarker data, the pharmacovigilance community will need to address some of the existing challenges (Table 1), including: to consistently gain access to these diverse and unstructured data sources; to evaluate the reliability and validity of each device and/or data type; to promote data standards that would allow harmonisation across devices and manufacturers; to integrate these data with other sources that could enhance insights; and to develop and agree to appropriate novel mathematical methodologies to analyse and interpret the data. This work is needed now to steer and consider how to capitalise best on this capability change. Nevertheless, pharmacovigilance organisations should monitor to truly assess the value of the data and not assume the value is there from the outset. Indeed, more ubiquitous data are not always more informative, although, particularly when combined with other data sources, they have the potential to offer improved insights. Ethical issues related to privacy, security, legal and informed consent will also need to be taken into account along with far reaching changes in how pharmacovigilance is conducted and how systems are maintained.[32] An additional consideration is the potential encouragement of an overly medicalised health culture, which in some instances can impact patient health negatively by inducing a false sense of security that could result in patients and physicians not looking for signs of AE (e.g., when monitored for atrial fibrillation patients

TABLE 1

Current key challenges and possible resolutions of digital biomarker use for post-licensure safety monitoring[a]

Current key challenges	Possible resolution
Data accuracy, reliability and/or validity: varying levels of validation for consumer devices make the data untrustworthy for medical decision-making	As technologies mature, those that are more scalable will become more accurate and reliable. As the various healthcare opportunities become clearer, large manufacturers can undertake stricter levels of validation
Lack of data standards: no consistency in the data provided across devices makes comparisons very difficult	When the value of the data is demonstrated, pharmacovigilance stakeholders can agree upon data standards; solution providers can adopt these standards to enhance their offering
Linkage to medication data and/or health records: digital data in isolation have limited value, and are currently not linked to medical history	Initially, data for 'high-risk patients' can be linked in large cohort studies; as health records and other data types become increasingly accessible to patients it will become easier to link them together
Data accessibility for algorithm implementation: device 'raw' data are not often accessible; most manufacturers do not have incentives to include pharmacovigilance-related algorithms	Large cohort and real-world evidence studies can allow early demonstration of data value; subsequently, and once there is consumer demand, manufacturers can incorporate algorithms on the devices or allow users access to raw data
Data interpretation: data are unstructured, highly variable and complex; there are currently no agreed standards for analysis	Pre-competitive collaborations can provide an efficient approach to facilitate standardisation of methodologies for data analysis and interpretation
Long-term compliance: longitudinal data are most relevant but long-term compliance with technologies is suboptimal	As consumers become more and more empowered to look after their own health, and as technologies become less intrusive, compliance is expected to improve
Regulatory considerations: there is no regulatory guidance on how to use and extract value from these data	When the value of these data is realised by pharmacovigilance stakeholders, health authorities will probably set guidance for its use
Socio-technical factors: the complex interrelation of socio-technical components is crucial for the successful implementation of digital biomarkers for safety monitoring alongside existing systems	Studies to gain insights into the various socio-technical factors will be needed before developing a robust model maximising probability of success of practical implementation. Additionally, careful planning for and measurement of impact will be necessary to identify unintended consequences and correct for as needed

[a] Note this does not intend to be an exhaustive list.

might not seek help for signs of a heart attack).

The socio-technical challenges that are involved in the design, development, implementation and use of health information technology within healthcare systems must not be ignored. A model developed by Sitting and Singh identified eight interrelated dimensions that largely account for the success of new health information technology interventions[33]: hardware and/or software, clinical content, user interface, people, workflow, organisational policies, external rules, and system monitoring. Successful implementation of digital biomarkers for pharmacovigilance would initially require qualitative studies to gain insights into such socio-technical dimensions because previous experience shows that problems often arise in several (sometimes all) of them.[34] Planning for and measuring the impact of new technologies is clearly important as is the careful measurement of unintended consequences as needed.

Adverse drug or vaccine reactions can be classified by frequency on a spectrum from 'very common' (≥1/10) in magnitudes of 10 through 'common', 'uncommon/infrequent' and 'rare' to 'very rare' (<1/10 000).[35] Pharmacovigilance requires the ability to detect effects across this frequency spectrum including rare outcomes, particularly when they can heavily impact the benefit:risk of drugs or vaccines and therefore their appropriate use. Effective safety surveillance requires rapid access to strong, accurate and granular data to better understand the AE as well as how or when drugs or vaccines have been used. Understanding the severity of the treated disease and its manifestation as well as potential confounding factors (e.g., dietary, sleep patterns and level of physical activity) is important. Across all these areas, albeit to varying extents, digital biomarkers have the potential to help when used appropriately. Three particular areas of opportunity exist: (i) 'targeted surveillance' – proactively looking for outcomes known to be frequently associated with drugs and with limited background incidence or where there is suspicion that such an AE might occur and there is a need to ensure that it does not occur more often or severely or seriously than anticipated. Monitoring arrythmias using wearable devices or utilising a mobile phone camera to detect adverse cutaneous reactions, as described in cases two and three, could be examples of this; (ii) 'identification of previously unknown events' – events that are not known to exist because the data are not currently easily available or no prior suspicion exists. Food consumption and/or weight change or sleep patterns as discussed in case four could serve as examples of this; and (iii) 'provision of more insights into factors potentially causally associated to known AE' – the potential role of confounders such as physical activity, diet, among others. In all scenarios, validation is key, so that a tidal wave of AEs that have minimal importance is not created.

Owing to the initial variability of the data and lack of reliability, trustworthiness and standards for validation of consumer-grade devices, at least initially, one can obtain 'population' (rather than 'individual') safety insights; in other words, it might be difficult to suggest that one individual patient is having a low-severity event but at a population level the trends observed can be meaningful. For example, if one patient loses weight it is not possible, individually, to establish causality (perhaps the patient is on a diet); but at a population level this might be an important finding if a particular drug has an impact on weight. Even for well-known AEs (e.g., arrythmias) the somewhat limited device and/or algorithm reliability would make it difficult to gain individual

patient insights but would enable population-level assessments. Zhu *et al.* recently described the potential of smart wearable devices with cardiac monitoring capabilities to detect cardiac AEs associated with antipsychotic drugs.[36] The current unpredictable nature of these cardiac events has led to a restriction of drug use that might have been avoided through more robust monitoring at population level.

Wearable device data are not limited to activity and pulse rate. Increasingly other measures and physiological variables are also determined, including location, blood oxygen saturation or blood pressure, all having the potential to offer additional safety-related information. Several well-known adverse effects of medication result in changes in the aforementioned variables. For example, cytokine release syndrome resulting from immunotherapy typically presents symptoms such as fever, hypotension or hypoxia,[37] most of which could be amenable to being measured with wearable devices. These could therefore enable identifying cytokine release syndrome events early and remotely, minimising hospitalisation time after therapy.

Concluding remarks

Although digital biomarkers are often used in randomised controlled clinical trials, their value is not yet widely considered for safety monitoring. However, as highlighted, many opportunities exist to utilise this data type to enable better understanding of medicinal safety outcomes. We desire and anticipate much wider use of digital approaches in medicinal safety. We expect these to enable more granular and personalised understanding of safety and better safety profiling and therefore prevention. However, to crystallise the multiple opportunities that exist, pharmacovigilance stakeholders must still overcome the existing barriers that prevent widespread utilisation, the greatest of which arguably relates to data limitations (management, standardisation, quality, analytics, validation of consumer-grade apparatus measurements, etc.).

We do not expect digital biomarker data to replace traditional data sources for safety surveillance. These data sources have strengths that are complementary: spontaneous safety reports are international and capture suspicion and the rationale for clinical or patient suspicion, and health records data from traditional health systems have high veracity; digital biomarker data capture is faster, richer and continuous, and has the potential to address the gap that currently exists between healthcare provider visits to drive new safety insights. Hence, the combination of these data types is expected to enable more robust patient monitoring systems.

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Data availability

No data was used for the research described in the article.

Declaration of Conflicts of interest

LG-G and AB are employees of the GSK group of companies and hold stocks and shares, and declare no non-financial relationships and activities.

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