IMI1 Final Project Report Public Summary

Project Acronym: WEB-RADR

Project Title: Recognising Adverse Drug Reactions

Grant Agreement: 115632
Project Duration: 01/09/2014 - 31/12/2017

1. Executive summary

1.1. Project rationale and overall objectives of the project

The WEB-RADR project was developed in response to the rapid adoption of smartphones, mobile applications (apps) and social media to discuss health and medicine issues. The project aimed to utilise the power of social media and new technologies to determine whether these novel data sources add value to existing pharmacovigilance methodologies and develop policy recommendations for their use.

Reporting of Adverse Drug Reactions (ADRs) by mobile devices and the use of social media analytics tools for pharmacovigilance were new and unexplored concepts. WEB-RADR intended to develop a mobile reporting app and evaluate its utility both from user and pharmacovigilance perspectives before making a package available for adoption across the European Union (EU) network.

The vast amount of information generated through social media required a well-defined approach for monitoring, reporting, analysing and evaluating suspected ADRs relating to medicines which was developed through WEB-RADR. The impact on healthcare professional (HCPs) and patients, and their behaviour towards the use of medicines was analysed, together with the value of the information to pharmacovigilance.

Alongside development and assessment of the technology and data described, the project was designed to develop policy recommendations for their future use based upon their value from a pharmacovigilance perspective.

1.2. Overall deliverables of the project

The project was set up in five work areas comprising project management, two technology development and evaluation work packages (one for social media and the other for mobile apps) and a work package responsible for evaluating their value to pharmacovigilance. Encompassing the core delivery Work Packages was a governance and policy Work Package with the remit to both ensure the project operated within existing regulatory frameworks and to make new policy recommendations based upon the research conducted.

The governance and policy Work Package (WP1) developed policy recommendations and frameworks for the use of mobile devices for the reporting of ADRs and social media for the safety monitoring of medicines. Assessment of the ethical and societal considerations, and personal data protection legislation requirements, for such tools was undertaken.

The social media and analytic work was carried out by Work Packages 2A and 2B. Key outputs included creation of an analytics dashboard and collaborative workspace for visualising classified social media data. Analysis was carried out through implementation and evaluation of social media through three streams (1) ADR detection, (2) record linkage, and (3) safety signal detection.

Work Packages 3A and 3B undertook work on the WEB-RADR mobile reporting platform, which was made available in three Member States, UK (Yellow Card), the Netherlands (LAREB), and Croatia (HALMED). An instruction manual and online portal for additional Member State adoption of the mobile was created, and electronic health record connectivity accomplished. Associated user-based evaluation provided insight into barriers and facilitators to using a mobile app for reporting ADRs and its value as a tool for providing drug (safety) information. Two-way communication of risk information was explored within target populations and patient-friendly reporting terms founded.

Scientific impact evaluation was carried out by Work Package 4 who compared mobile app reports received with those from conventional channels. A new algorithm to measure and assess the quality of reports received was developed and app reports were cross-checked with primary medical notes for quality. The contribution of mobile app reports to signal detection and the identification of safety signals was explored. The utility of social media as a statistical safety signal detection source for detecting earlier and/or different signals, as well as gaining additional insights into signals has been examined.

The project management and communication Work Package, WP5, formed communication plans and financial guidance documents for the project consortium. Communication and dissemination of information regarding project progress and outputs was achieved via a range of means; website and social media publicity, event organisation and conference participation. A sustainability plan was created to ensure longevity of the WEB-RADR outputs, including the mobile app platform. Project updates were communicated to IMI through yearly progress reports.

1.3. Summary of progress versus plan since last period

Over the final period of the WEB-RADR Joint Undertaking, information gathered over the course of the project on the use and value of social media and mobile technologies for pharmacovigilance, was finalised. Scientific and policy recommendations from work packages were agreed and output documents written, reflecting the work progress and results, and evaluation activities undertaken.

WEB-RADR Work Package 1 established clear policy recommendations and guidance on the approach and handling of data created on social media sites and the use of mobile technology for pharmacovigilance. A framework for ethical and data considerations addresses the various needs and

concerns of stakeholders while further modernising pharmacovigilance practices. Recommendations resulting from the project have been put forward to the EMA to inform the development of further guidance as part of the Good Pharmacovigilance Practices (GVP).

Work Packages 2A and B focused on integrated analytics of social media data from the analysis platform. This was addressed by three work streams; signal detection, adverse event recognition, and record linkage. The WEB-RADR Time Indexed Reference Dataset (TIRD) was created and used to compare VigiBase with social media. The WEB-RADR analysis framework was applied to social media data and put in context of MedDRA. The WEB-RADR reference set for AE recognition can be used to assess sensitivity of AE identification algorithms.

The user-friendly WEB-RADR mobile app developed by Work Package 3A, originally deployed in the United Kingdom, the Netherlands and Croatia, has subsequently been launched in Burkina Faso and Zambia through World Health Organisation (WHO) collaboration. The apps facilitate direct and instant reporting of suspected ADRs by patients, HCPs and the public, to their National Competent Authority (NCA). The apps also communicate accurate, timely and up-to-date pharmacovigilance information to users, and permits the submission of ADR reports whilst offline.

Further work by Work Package 3B on the value of a mobile app as a tool for two-way communication was explored in a pilot study aimed to assess and evaluate patients' perspectives on patient-friendly Medical Dictionary for Regulatory Activities (MedDRA®) terms in ADR reporting forms.

WEB-RADR Work Package 4's Open Reference Standard and Signal Before Detect Algorithms were finalised. Limited utility of social media as a broad-based stand-alone statistical safety signal detection store was found. However social media "hot spots" (niche areas) have been identified where social media could aid signal detection. WEB-RADR app reports characteristics, quality and contribution to signal detection were assessed using the clinical documentation tool developed by WP4 (LAREB, Netherlands).

Work Package 5 have focused on project output sustainability and dissemination of the project results by means of the final Stakeholder Event.

There were no major deviations to scheduled work. An amendment was made to the Description of Work in August 2017, requesting a four-month project extension to 30/12/2017 and the addition of a sustainability deliverable.

1.4. Significant achievements since last report

Significant developments over the third and final reporting period for WEB-RADR include:

1.4.1 Stakeholder Event – The WEB-RADR Stakeholder Event took place on 7 September 2017 in London. The one-day event provided an overview of WEB-RADR's outputs and its contribution to the safeguarding of public health within the European Union network and beyond. The event slogan, "Are we ready for the new vigilance world?", highlighted the achievements of the project and called participants to exchange views and ideas for building on the future of pharmacovigilance in the digital age, as well as promoting the mechanism by which the project deliverables would be sustained.

1.4.2 WEB-RADR beyond the EU – Through collaboration between IMI, WEB-RADR and WHO, the WEB-RADR mobile application was launched in Burkina Faso and Zambia for the reporting of suspected adverse drug reactions (ADRs). The WEB-RADR team worked together with ZAMRA (Zambia Medicines Regulatory Authority) and the Burkina Faso medicines agency DGPML (Direction Générale de la Pharmacie, du médicament et des laboratoires) to adapt and tailor the app for country specific needs; branding and language requirements. Communication brochures and e-materials were produced in collaboration with Upsala Monitoring Centre (UMC) for the launch events and disseminated in country hospitals. A number of articles and newspapers published items in both countries and the Zambia launch was broadcast on National Television and the ZAMRA website.

1.4.3 Sustainability model – The WEB-RADR sustainability plan was developed over the third reporting period. The concept plan comprised three core themes under which WEB-RADR delivered outputs; (1) policy and guidance, (2) technology maintenance and development, (3) building on research conducted within WEB-RADR. With each theme having different sustainability considerations, a more detailed WEB-RADR sustainability model was developed from the initial the concept plan. As part of this model, the WEB-RADR Management Board was established and held its first meeting. The Board's aim is to ensure nurturing, protection and development of the mobile application platform beyond the WEB-RADR project to ensure continuity of services and development of a commercial model for the mobile application and its underlying platform.

1.4.4 Policy recommendations - Work Package 1 has delivered policy recommendations for the use of social media and mobile apps in pharmacovigilance beyond the project. The team have discussed emerging regulatory questions associated with the use of social media in the context of pharmacovigilance which, alongside data gleaned from the project have enabled them to develop recommendations. These will be used in 2018 to inform the development of further guidance as part

of the Good Pharmacovigilance Practices (GVP), which provide guidance to implementation of the EU regulatory framework. A risk-based approach has been applied in the development of the recommendations on the use of social media in pharmacovigilance. This should allow for a better utilisation of this new data source but also ensure continuous monitoring of the safety of medicines and a timely identification of potential safety issues without overburdening established pharmacovigilance systems.

Work Package 1 has also produced a set of recommendations for the development and use of mobile apps for easier, faster and more user-friendly reporting by patients, consumers and HCPs and access to collected reports for signal detection purposes in the context of pharmacovigilance.

1.4.5 Recommendation papers - Recommendations from the social media and mobile application work conducted over the three years of the project has formed two recommendation papers, one for each work area. Work Package Leaders and other members from the WEB-RADR consortium contributed to the development of these papers. Each paper will provide considerations, rationales, caveats and suggested areas for potential further research. The recommendation papers will be published shortly after the project completion.

1.4.6 WEB-RADR 2 – The WEB-RADR project was successful in the IMI2 Call 11 bid on the exploitation of IMI project results. A positive evaluation was received in January 2018, and the project was awarded the entirety of its funding request. WEB-RADR 2 consortium partners will work together to progress the project documentation.

1.5. Scientific and technical results/foregrounds of the project

Mobile Apps:

The mobile application developed by WEB-RADR has been launched within Europe - the UK (MHRA Yellow Card), the Netherlands (LAREB Bijwerking) and Croatia (HALMED), and beyond Europe – Burkina Faso and Zambia. The EU apps were downloaded over 10,000 times, with positive feedback around the news and data functionality provided. Reporting rates via the mobile app in the EU were not significant compared to other routes, however a marked increased rate of reporting of suspected ADRs were seen in both African countries following the launch of the mobile apps. Tailored news feeds of medicines information, watch lists allowing tracking of medicines of interest, and the ability to complete and submit ADR reports whilst offline, has proven successful.

There has been significant positive feedback and interest in adoption of the mobile app platform, an extension of the mobile app functionality to expand access and reach of the information within it.

Specifically, a number of organisations have approached the project to explore the potential for integration of functions of the WEB-RADR app into their own offerings. This resulted in a project concept paper called 'WEB-RADR as a platform'. This concept was the precursor to our proposal for exploitation call funding and will now be developed through the WEB-RADR 2 project, exploiting the results and outputs of WEB-RADR.

Studies conducted by Work Package 3B (User Based Evaluation) have shown that mobile reporting apps such as that developed in WEB-RADR are highly valuable to HCPs and patients. User research gave insight into user preferences; terminology (different terminology should be used for patients and HCPs), speed (a mobile app should be a faster, easier way to report ADRs than other reporting options), acknowledgment and feedback (confirming receipt and tailoring of feedback options), trustworthiness (the organisation linked to the app should be familiar, trusted by its users), login (automatic login, time period for login).

There is significant value in mobile reporting apps and the launch of the WEB-RADR app in Burkina Faso and Zambia, through collaboration with WHO, has demonstrated this. Alongside a concerted promotional effect by local pharmacovigilance centres the WEB-RADR mobile app proved a low cost mechanism to facilitate collection of ADR data in areas where it hadn't previously been feasible. It also provided a means of free and instant access to medicines safety information and a quick and easy method of reporting side effects directly to regulatory agencies, whilst also being able to use the app without Internet.

A sub-team of Work Package 4 studied WEB-RADR app reports characteristics, quality and contribution to signal detection. Mobile app report characteristics were seen to be similar to reports received through conventional means. The clinical quality of app reports was close to those from conventional means, however the completeness of app reports was slightly lower as was expected due to the streamlined nature of the reporting form developed with patient feedback through the project. Mobile app reports from MHRA (United Kingdom), LAREB (Netherlands) and HALMED (Croatia) were demonstrated to have contributed to validated signals and had relevant and useful drug-event information. Development and testing of the clinical documentation tool developed by WP4 (LAREB, Netherlands) has been published in Drug Safety.

Social Media:

Work Package 2A developed a collaborative workspace for visualizing and analysing social media data pertaining to products selected by WEB-RADR partners. To meet this objective, the Epidemico's

MedWatcher Social platform was adapted to monitor WEB-RADR products in three European languages – English, French, and Spanish. The social media monitoring platform was designed to utilise publicly available data from Internet social media sources. For WEB-RADR data from Twitter, Facebook (from 2012-2015), and latterly Reddit and the Inspire patient forum were made available. The tool was designed to complement existing safety practice by supporting post-marketing safety surveillance. Filtering and classification algorithms are applied to identify content relating to adverse event experiences with medical products. The filtered, de-identified, and aggregated data are then made available to end users for review and analysis via an interactive web-based visualisation dashboard.

WEB-RADR looked at the potential value in using social media for pharmacovigilance and aimed to address the role of social media in signal detection and signal confirmation practice. The WP2B and WP4 sub-teams focused on the adverse event recognition, record linkage, signal detection, combining data from different sources, and tools for assessing social media.

Two reference standard data sets were created, the WEB-RADR Time Indexed Reference Dataset (TIRD) and WEB-RADR Open Reference Standard. The TIRD was based on early signals detected in the context of drugs manufactured by EFPIA partners (WP2B) and was used to compare VigiBase with social media, looking at the occurrence of first post in social media relative to the index date of a positive control. Different indicator score thresholds were applied and performance analysed. Looking at social media signals, there were three positive controls in the social media 0.4 dataset that would have contributed to the evidence of the PEC being a safety signal. The WEB-RADR analysis framework was applied to social media data and put in context of MedDRA. When historical verbatim VigiBase data was added to MedDRA mappings, sensitivity was doubled. The WEB-RADR reference set for AE recognition can be used to assess sensitivity of AE identification algorithms. VigiMatch algorithm was adapted to social media record linkage based on verbatim text and had >95% precision.

The WEB-RADR Open Reference Standard (WP4) has been generated by extracting information from the labels that can be freely downloaded from the FDA website and which relate to products manufactured by the EFPIA partners (the same products used in the context of TIRD). The Open Reference Standard will be made publicly available, such that people outside the consortium can benefit from its existence. The signal detection work stream, by use of the Signal Before Detect algorithm developed within the project, has found limited utility of social media as a broad-based stand-alone statistical safety signal detection store. However, niche areas have been identified where social media could play either a stand-alone or signal-enriching role. Social media hot spots have been

identified as PTs "skin discomfort", "drug tolerance", "elevated mood". The utility of social media for broad signal detection, as a standalone or a complementary data source, has yet to be determined.

1.6. Potential impact and main dissemination activities and exploitation of results

Socio-economics benefits and contribution to the health of European citizens

The WEB-RADR project was the first initiative of its kind that has been established in Europe to utilise the powers of social media and new technologies for pharmacovigilance purposes. Mobile applications offer a realistic possibility of developing systems for real-time pharmacovigilance and for near instantaneous transmission of important information related to the safety of medicines directly to national competent authorities and thus promoting better treatment decisions for EU citizens.

WEB-RADR has been successful in developing a mobile platform for reporting of ADRs and for communication of safety information to HCPs and patients. The WEB-RADR aim was to empower patients and HCPs to report ADRs, and to provide app users with accurate, timely and up-to-date safety information regarding medicines. These goals have been achieved and over the final year of the project, the WEB-RADR team has been able to improve the mobile app user interface and back end systems to improve scalability, and utilise more modern programming techniques. The mobile app has been developed and its functionality enhanced. The app code for iOS and Android versions have been harmonised into a single code base making future updates to the app easier and more stable. This will also deliver enhancements to the look and feel of the application giving the user a better app experience and aid them in their reporting experience or when they are looking for more information about medicines issued by national regulatory agencies.

The project has also demonstrated niche areas where review of social media data may be beneficial to public health. Because the research of the project has highlighted specific areas of interest/ value we have been able to deliver risk proportionate policy recommendations for use. This addresses one of the core concerns both the pharmaceutical industry and regulators that regulatory requirements for social media data to be treated in the same way as spontaneously reported cases would both stifle innovation, and more significantly have potential to reduce the effectiveness of traditional signal detection systems.

Increase the competitiveness of Europe

The industry leading nature of the work of the project has led to many international requests for presentations and information about the project. Indeed, we have been informed that a number of

regions have been awaiting the results and recommendations of WEB-RADR prior to developing their own guidance. WEB-RADR has, uniquely in this area, been able to take a data and impact driven approach to policy recommendations, which through provision of the recommendations to the EU regulatory framework and their subsequent adoption later this year puts the EU as the world leader in this area.

The pragmatic nature of the social media recommendations eliminates unnecessary burden on industry, whilst facilitating use of new technology to detect safety issues, and ultimately improve patient health outcomes in the EU. The success of the mobile apps, particularly in strengthening developing pharmacovigilance systems also presents future opportunities to EU pharmaceutical industry to launch novel products in territories which wouldn't otherwise have been feasible. For the regulatory system this approach to data collection potentially means the availability of more robust safety data prior to EU product launches.

The consortium has actively publicised the project outputs through the EU Pharmacovigilance network, as well as through international conferences. Furthermore, the WEB-RADR project is going to publish the results and impact of the deliverables in peer reviewed scientific journals in order to sustain the impact of the research. The project is committed to publishing and making available datasets used for the research where this is legally feasible to enable other researchers to continue the activities covered in the project.

Platform exploitation

Experience has shown that users are focusing primarily on the news and data functions of the app with only occasional use of the reporting functionality. From knowing this, the team has thought about how best to improve the user experience and availability of information. Through the IMI call 11, WEB-RADR 2 will build on the current app functionality by making the functionality available through application programming interfaces (APIs). This will allow third party organisations to embed WEB-RADR platform functionality into their own systems, applications and websites. The potential impact of the WEB-RADR platform is to significantly increase access to, and use of both EU ADR reporting systems, and the knowledge and insights that arise from the data and the broader pharmacovigilance system.

The app front-end systems have wide applicability, serving as a convenient option for reporting and information distribution through NCAs reporting systems. During the 18-month WEB-RADR 2 project, it is intended that the API components of the mobile app platform are made available in three EU countries (Denmark, Netherlands and United Kingdom). Included within the work plan will be adaption

of the existing WEB-RADR Management Board subscription model to enable wider adoption of the tools as they become available. This will deliver sustainability of the different offerings on the platform depending on the needs of the countries proposing to adopt the technology to a model that is not reliant on funding from outside the user base beyond the duration of the exploitation call. Importantly WEB-RADR's existing maintenance arrangement foresees fluctuations in technical development of the app, and as such the delivery team is able to rapidly add resources to the project to support additional roll out as required.

The exploitation call will enable the WEB-RADR tools to go significantly beyond the existing offering, making it both more attractive and reaching larger numbers of European citizens than would otherwise be feasible. It is envisaged that by the end of the project the platform could deliver a complete ADR reporting system for an NCA, including app, mobile responsive, web-based and integrated healthcare system reporting in a low-cost package.

Moreover, the tools will be available to support Marketing Authorisation Holders (MAHs) in fulfilling risk minimisation commitments in EU Risk Management Plans, or for integration of regulatory services into patient support programmes (PSPs), thereby reducing the financial burden of those requirements on industry. The tools that will be delivered will adhere to standards defined in EU legislation for reporting of ADRs, with systems designed from source to comply with the EU General Data Protection Regulation (GDPR).

1.7. Lessons learned and further opportunities for research

Consortium of EFPIA and public partners

The WEB-RADR project has seen fantastic collaboration between both EFPIA and public partners. With regular meetings led by enthusiastic Work Package Leads and Steering Committee members, progress of the project has been carefully tracked, advice sought where required and risks managed. The expertise of the General Advisory Board has provided the project with the necessary guidance and support. The WEB-RADR consortium has reviewed contributions (time and workload) over the course of the project and reallocated tasks to best distribute workload according to partners capabilities. The success of the WEB-RADR was through using the practical experience and skills already available in the network. Led by a consortium of world-leading experts from industry, regulatory agencies, and academia, the project has delivered a variety of tools and outputs, all of which are effective and supportive of pharmacovigilance practices in the EU network. Another success factor was the keenness of those involved to make best use of the opportunity and drive pharmacovigilance innovations. The partnership within this project has driven the project's success and together identified further
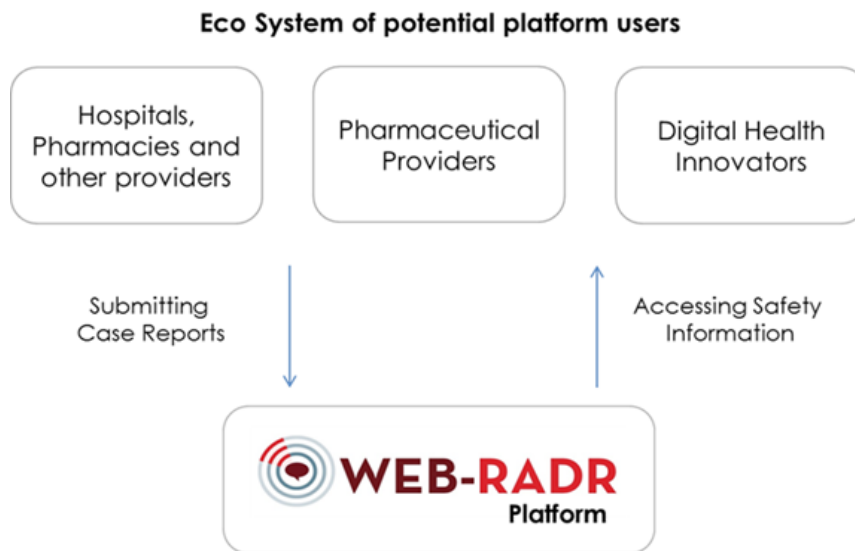
opportunities to contribute to the EU health field and advance the project's outputs, making them sustainable and re-usable.

There were some areas of the project where it was easier to enable EFPIA participation than others. Specifically, EFPIA partners were highly engaged and active with the scientific research and policy areas, whilst contribution to technical development was more challenging because of the infrastructure used. However, this not adversely impact deliverables since EFPIA colleagues remained engaged with reviewing and documenting the outputs. Additionally, EFPIA partners were able to flex the resources that they contributed, to progress areas of the project that were moving slower than anticipated and to focus on additional deliverables such as the project recommendations papers. Success of this approach adopted is demonstrated by timely completion of deliverables and EFPIA interest in adoption of the mobile app platform through the WEB-RADR2 project.

Further advancing the field

WEB-RADR has explored modification of the technology outputs of the project; the social media monitoring platform and mobile applications. It is intended that the mobile app will not exist as an independent closed application but instead have documented application programming interfaces (APIs) that would enable the wider stakeholder community to link their own application components to these WEB-RADR software. The availability of such APIs greatly extends the utility of the underlying systems, increasing visibility, and is instrumental in making these systems a core part of the development of related applications. The API functionality will have a significant positive impact on sustaining the original ideas, concepts, methods, and tools developed within WEB-RADR. Exploitation of its APIs will enable the functionality to be embedded directly into apps, websites and forums that HCPs and patients use on a day to day basis. This would mean that ADR reporting functionality can be enabled within apps supporting the healthcare network, or by electronic health record (EHR) providers. Equally, the platform will enable components to be re-used by the pharmaceutical industry where regulatory information about a product(s) may be made available in apps developed by the pharmaceutical industry in support of new products as part of patient support programmes (PSPs) or educational materials. Through collaboration and partnership with pharmaceutical industry participants of the WEB-RADR project, it was evident that there was significant interest and potential value in modifying and repurposing the mobile app tools for industry use.

The WEB-RADR project's public private partnership (PPP) has formed the foundation of the WEB-RADR platform; to allow WEB-RADR to provide services to the wider health network and for the technology to be sustainable. The below figure demonstrates the ecosystem of potential platform users.

Eco System of potential platform users

In developing the WEB-RADR platform, the benefits of the project would extend beyond the lifetime of the project and provide the digital health community with clear models for interacting with medicines regulators, and position WEB-RADR as the central hub of digital transactions for pharmacovigilance.

Another key aspect identified for further research is integration of the WEB-RADR mobile app into the healthcare network. The existing mobile app successfully integrates patient and HCP reported ADRs into the regulatory network, but there is currently no electronic mechanism to add this to the patient's care record. In addition, regulatory news feeds are currently available within the app however these are not presented to a HCP at the point they prescribe, dispense or administer a medicine to a patient. There is a clear need for this information to be made available to the healthcare network to aid the clinical decision-making process. In order to achieve this, regulatory terminologies and terminologies used in healthcare must be mapped to enable the platforms to 'talk the same language'. In addition, connectivity protocols with EHR databases are needed so that information can be accurately drawn from the EHR to support reporting of ADRs and regulatory information can then be made available in the care record. This section of further research will also be conducted within the WEB-RADR2 project and enhance the WEB-RADR platform as the central hub of digital transactions for drug safety.