Theme 3: Sustainability and future opportunities

WEB-RADR Stakeholder Event
7 September 2017
The social media impact for patients
François Houýez, EURORDIS

WEB-RADR app in Burkina Faso & Zambia
Shanthi Pal, World Health Organisation

Sustainability of WEB-RADR’s outputs
Phil Tregunno, MHRA
The social media impact for patients
François Houÿez, EURORDIS

WEB-RADR Stakeholder Event
7 September 2017
Social networks and medicines: what’s of interest to patients (and also for pharmacovigilance experts, industry)?

- To learn on a class of products or a disease
  - The state of the art of clinical care and care management as discussed by patients
  - The identifications of patients difficulties, their unmet needs
  - How patients evaluate compare different products to treat their disease
  - To learn on the impact of the medicine in patients’ life, confirm or deny efficacy claims

- To understand the drivers of treatment observance
  - Whether patients stop treatment, and reasons why, or change dosage
  - Same for patients who never started treatment

- To learn on other possible uses, appropriate uses, misuses, off-label uses...
  - Drug-drug interactions
  - Illicit products and medicines
  - Benefits of off-label uses, and their safety...
Social networks and medicines: what’s of interest to patients (and also for pharmacovigilance experts, industry)?

• To anticipate pharmacovigilance signals, faster detection / other concerns
  • Understanding language used to describe products/AES pairs = facilitates present and future communication
  • Detecting new signals early, or confirming signals observed elsewhere
  • Analysing relation between posts and time (seasonal effects, press campaigns...)
  • Seeing which terms are commonly associated, e.g. concern about a product and its excipients
  • Analysing if and how patients discuss risk minimisation measures, their acceptance, or how they try to bypass them, or if they received safety information / risk communication (impact assessment)
  • Localising: e.g. higher antalgic dependence / excess of antalgic use in the area of a specific hospital
  • Learning what patients do to alleviate the symptoms with self-medication (e.g. active carbon and bloating)
Activity of interest for patients

Other discussions

• Drug-”recreational products“ interactions, how to use them, risks
  • European Monitoring Centre for Drug and Drug Addiction (EMCDDA): 560 active substances on the EU market
• Life-style habits that exacerbate ADR and/or affect efficacy
  • E.g. some food to be avoided
• Exposure during pregnancy
  • Sharing treatment experiences with other women
• Medicine shortages, end of a shortage
  • Searching patients in greatest need to whom I could pass my own supply
• Emergency need of drug supply
  • HIV infection prevention, need for Prep treatment and prescription outdated
What can we detect?

- So far, analysis of social media focused on:
  - Medicines used by large numbers of patients
  - Frequent events
  - General social networks with many users (Facebook, Twitter..)

- As a proof-of-concept research: with the web-RADR tools we have, can we detect life on earth from space?
  - Other rarer events or medicines used less frequently or more specific networks to be analysed later

- Main findings
  - Web-RADR:
    - Automated process: 88% sensitivity, 70% positive predictive value
    - Average detection performance is interesting, varies by product
    - Earlier signals in social networks than MAH databases?
  - Other research: signals from social networks earlier than in institutional databases (more than 30% of signals are identified in average 75 days earlier than in FAERS, Vigibase - Detec’t, in press)
Initial Assessment of Social Media’s Utility

Increased Volume of Mentions does not Appear to Correlate with Label Changes

October → November – academic work, cold season, contributing to increase mentions

March → April – academic work contributing to increase

1. Peripheral Vasculopathy & Raynaud’s
2. Increased erections/priapism
3. Stimulants and Rhabdomyolysis
Initial Assessment of Social Media’s Utility

PT Comparison

Relative Percentages for 20 Common PTs

<table>
<thead>
<tr>
<th>PT</th>
<th>Epidemico Percentage</th>
<th>Vigibase Percentage</th>
</tr>
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<tbody>
<tr>
<td>Drug Ineffective</td>
<td></td>
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<tr>
<td>Pain</td>
<td></td>
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<tr>
<td>Altered State Of Consciousness</td>
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<tr>
<td>Somnolence</td>
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<tr>
<td>Nonspecific Reaction</td>
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<td>Insomnia</td>
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<td>Fatigue</td>
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<td>Malaise</td>
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<td>Headache</td>
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<td>Dizziness</td>
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<td>Nausea</td>
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<tr>
<td>Migraine</td>
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<tr>
<td>Feeling Abnormal</td>
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<tr>
<td>Rash</td>
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<tr>
<td>Fructose</td>
<td></td>
<td></td>
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<tr>
<td>Death</td>
<td></td>
<td></td>
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<tr>
<td>Weight Decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incorrect Dose Administered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition Aggravated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td></td>
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</tbody>
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Ratio of Epidemico and Vigibase Counts

<table>
<thead>
<tr>
<th>PT</th>
<th>Ratio</th>
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<tr>
<td>Injection</td>
<td>279.000000</td>
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<tr>
<td>Nonspecific Reaction</td>
<td>231.545455</td>
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<tr>
<td>Prescription Form Tampering</td>
<td>149.333333</td>
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<tr>
<td>Abdominal Symptom</td>
<td>48.857143</td>
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<tr>
<td>Therapy Change</td>
<td>23.432432</td>
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<tr>
<td>Drug Tolerance</td>
<td>21.410924</td>
</tr>
<tr>
<td>Elevated Mood</td>
<td>20.000000</td>
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<tr>
<td>Skin Discomfort</td>
<td>15.840000</td>
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<tr>
<td>Dependence</td>
<td>13.362069</td>
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<td>Alcohol Use</td>
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<td>Altered State Of Consciousness</td>
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<tr>
<td>Pigmentation Disorder</td>
<td>9.986977</td>
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<tr>
<td>Drug Diversion</td>
<td>7.687500</td>
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<tr>
<td>Abnormal Dreams</td>
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<td>Attention Deficit/Hyperactivity Disorder</td>
<td>4.589434</td>
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<tr>
<td>Medical Device Removal</td>
<td>4.000000</td>
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<tr>
<td>Feeling Of Relaxation</td>
<td>3.888889</td>
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<tr>
<td>Affect Lability</td>
<td>3.681481</td>
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<tr>
<td>Withdrawal Syndrome</td>
<td>2.821429</td>
</tr>
<tr>
<td>Trigeminal Neuralgia</td>
<td>2.477778</td>
</tr>
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</table>
Detection of off-label use, e.g. misoprostol (Medical topics mentioned excluding topics related to the MA)


Analyses of posts on social networks
“Pregnancy complications and puerperal and perinatal infections” representing 12 to 24% of posts over 10 years

Detec’t, Dr Stephane Schutz
Detecting small objects

**Life-compatible Planets in space**

To detect a signal which is

- Constant (continuously sent over a very long period of time with no or little variation, as a wave with some regularity)
- And using the same vehicle (x-rays, photons etc.)
- If you can’t detect it, someone else in the next months or years will detect it

**Rarer adverse event, or unexpected one, of for medicines less often used**

- Intensity of data emission is not constant, comes in unexpected batches, no regularity, no predictability
- Vehicle varies constantly
  - If no reaction on a social network, patient will use another one, until someone replies
- Emitters can use multiple vehicles simultaneously (duplicates)
- External factors influence the start of emission, or the quantity
- See example →
Levothyrox new formulation arrives (excipient change)

Traffic on social networks of patients treated with levothyroxine, France

- Since 08/2013: traffic dominated by posts on shortages
  - Shortage high on the health agenda / health authorities. “Someone cares for us at the MofH”
  - EudraVigilance: high numbers of ADRs reports probably more in relation with the shortage (no tool for patients to report on shortages) Banovac, Arlett, Haerry, Houyez et al, Patient reporting in the EU: Analysis of Eudravigilance data Drug Safety 2017 Apr 17

- 04/2016: Tchernobyl 30 years later
  For the patients’ group, the increased used of levothyroxine in France after 1986 was a direct proof of a Tchernobyl effect, even if supreme court ruled out any impact of Tchernobyl on thyroid cancer incidence

- 04/2017: a new formulation available – bioequivalence studies
- 17/08/2017: complains from patients / side effects
- 21/08/2017: petition with 68 000 signatures, appearing in all general media
- 23/08/2017: 76 000 signatures, social networks did not comments the ANSM communication (only their free call number), no comments on doctors’ views that effects are only transient
  - “SFR news”: Question from one Senator to the President of the French Republic.
  - “Le Nouvel Observateur”: association announced that if no action from authorities, patients would march on the National Assembly and bring the case to WHO
Traffic on social networks of patients treated with levothyroxine, France

- 24/08/2017: MAH explained fewer than 1% of users report side effects, not more than with the older formulation
- 24/08/2017, “Le Monde” calls for more patients to report
- 24/08/2017: on social networks, new accusation: in order to camouflage the side effects of generics, the ANSM must have ordered changes to the originator product to copy the side effects of the generics
- 25/08/2017: No return back to old formulation
- 25/08/2017, “Le Quotidien”: no need to panic
- 25/08/2017, social networks: Even greater scandal as product soon to be authorised by the EU
- 28/08/2017, “Elle”: Free call number submerged. Here's how to call
- 29/08/2017, “Sciences & Avenir”: Number of calls exploding: 70 000 calls (but not from 70 000 distinct people). Petition reaches 155 000 signatures
- 29/08/2017, social networks: Horrible patient stories with new Levothyrox
Traffic on social networks of patients treated with levothyroxine, France

- 29/08/2017, “Le Parisien”: Number of calls exploding. ANSM call centre team from 15 to 90 staff
- 29/08/2017, printed press: 160 000 signatures*, here’s where to add yours
- 29/08/2017, “Marie Claire”: Levothyrox: Do you know how much your life can be a hell?
- 30/08/2017, “Le Monde”: Patients decide to stop treatment
- 01/09/2017, “Nice Matin”: A first patient files a complaint for new Levothyrox endangering her life
- 5/09/2017, le Figaro Santé: 1500 severe ADR reports in the last two months. Centres saturated.
- 6/09/2017, Le Monde: Agnès Buzyn MofH, meets with patients org to calm down the crisis. No severe ADR reported.

*: representing 5% of 3 millions users
Lessons – pollution?

• Most reports provide no new information
• The flow “pollutes” the pharmacovigilance system
• Vicious self-sustaining circle, with articles in the general press nourishing posts on social networks, which themselves made patients more aggressive when interviewed by media
• A disease with recent controversies (Tchernobyl, shortage): special attention should have been given when introducing changes in new product

• How did it all start? Analysing how social networks initiated the discussions? What triggered the reaction of so many patients?
• How to stop such a campaign?
• What if something would be happening?
  • With this medicine?
  • With other medicines?
• Pharmacovigilance system saturated by reports on levothyroxine
  • Legal delays to report to Eudravigilance
Regulatory authorities already using them

To have a look at them on a case by case basis, more by curiosity

• 1997 – Yahoo forums
  • HIV products and lipodystrophy – FDA, EMA

• June 2009 – Familial Adenomatous Polyposis forums
  • Onsenal® market withdrawal – EMA

• 2009-2010 – H1N1 vaccine
  • Several agencies and MAHs consulted social networks in relation with safety concerns / mandatory vaccination

• November 2016
  • Scientific Committee ANSM – How to use these techniques for pharmacovigilance? Inserm, Kappa Santé, Kapcode, Web-RADR...

But more systematically?

• Ears in all directions?
  • Should we analyse all possible sources, continuously? In the event something occurs?

• Radars / algorithms focusing on some products / diseases?
  • Black triangle products?
  • Products with risk minimisation measures?
  • With post-authorisation safety studies?

• But you never know where a problem can be coming from
  • If these techniques have the potential to detect events earlier but are not used systematically, and something is missed: a new controversy?
Many other possible uses than signal detection

Discussions on social networks could be semi-guided, with questions to users, e.g. “how would you comment the changes in your life since you’re using product X?”

Analysing posts is one thing, establishing a two-way communication on social networks is another one. But why not?

Research is only beginning, needs to be continued. Call for an exchange of views between different teams using different approaches
Thank you. Questions?

francois.houyez@eurordis.org
Theme 3: Sustainability and future opportunities
The WEB RADR app in Burkina Faso and Zambia

Shanthi Pal
Group Lead, Medicines Safety
World Health Organization
Geneva
Safety & Vigilance in WHO

How it started

- Thalidomide 1961
- WHO Prgm. for Int. Drug Monitoring 1968

World Health Assembly Resolution **16.36 (1963)**

INVITES Member States to arrange for a systematic collection of information on serious adverse drug reactions observed during the development of a drug and, in particular, after its release for general use.
WHO Programme for International Drug Monitoring

1968
Africa joining the WHO Programme

1990

1995

2000

2005

2010

2015
Addressing the gap: African PV consultants for Africa

• Pharmacovigilance without borders

• Aim: to improve pharmacovigilance on the African continent by developing advanced drug safety capacities
PV of medicines of local relevance
PV Methods Spectrum

**Spontaneous Reporting**
- Denominator unknown
- Suspected ADRs
- All medicines

**Targeted Reporting**
- Denominator known
  - Suspected ADRs
  - Cohort specific medicines

  - Profile of ADRs for a specific medicine in a specific popn
  - AMPATH Kenya ARVs

- Denominator known
  - Specific ADRs
  - Cohort specific medicines

  - Incidence of a known ADR in a specific population
  - TSR of Tenofivir in Uganda

**Cohort Event Monitoring**
- Denominator known
  - All Events
  - Cohort specific medicines

  - Post-marketing surveillance of a new chemical entity
  - CEM of new antimalarials (ACTs)

**EHR Mining**
- Denominator known
  - All Events
  - All medicines

- Using data available in patient records to enhance PV

**Uganda**

**Ghana**

**Kenya**

**ARVs**

**Essential minimum reporting**

**Incidence of a known ADR in a specific population**

**Profile of ADRs for a specific medicine in a specific popn**

**TSR of Tenofivir in Uganda**

**CEM of new antimalarials (ACTs)**

**Post-marketing surveillance of a new chemical entity**

**Using data available in patient records to enhance PV**

**AMPATH Kenya ARVs**

**Uganda Ghana**
Expand the network of WHO Collaborating Centres

- WHO CC Nether-lands (2012)
- WHO CC Morocco (2010)
- WHO CC Ghana (2009)
- WHO CC Oslo
- WHO CC India (2017)
- UMC (1978)
Prioritize, harmonize

Minimum Requirements for a Functional Pharmacovigilance System

Introduction
Pharmacovigilance (PV) is defined as the “science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems”. It is a very important medical discipline to prevent drug-related adverse effects in humans, ensure patient safety and promote the rational use of drugs.

PV is well-established in most industrialized countries but its practice in low and middle-income countries is variable with some countries having absolutely no systems at all whilst a few have systems comparable to the best in industrialized countries. In view of the importance of pharmacovigilance to all countries, the World Health Organization, upon request from the Global Fund against AIDS, TB and Malaria (Global Fund) and key bilateral and technical agencies, has embarked upon an extensive and wide-ranging consultative process to produce a Pharmacovigilance Strategy for use by all countries that are seeking to advance PV systems, through the Global Fund and similar health initiatives. The process includes the identification of (and the specifications for) the minimum requirements for PV.

Countries using Vigiflow data management systems
WHO ICSR Database (VigiBase) Today

Total Number of Individual Case Safety Reports (ICSRs) in VigiBase

Number of ICSRs in VigiBase

Year

Region of Americas  European Region  Western Pacific Region  South-East Asia Region  African Region  Eastern Mediterranean Region
Very limited reporting from LMIC
Reporting statistics in LMIC

• In some countries
  • Average 0.106 reports/physician in 5 years
    • Disease burden overwhelms
      • Less than 3 minutes per patient
        • ADR Reporting not a priority

• Poor quality reports
  • Less than 30% include 50% of essential information
    • Negative impact on analysis
Barriers to end-to-end Pharmacovigilance
Snapshot: 3 Main problems

Main challenges
Limitations

A. Limited reporting
B. Low local capacity / capability to analyze data collected
C. Low NRA capacity / capability to take action from alert signals received: Only a small fraction (3 in 55 according to 2010 survey by WHO) of the NRAs regularly take specific actions from signals received; most of these decisions are a replication of what was done by the SRAs.
A majority of the products will be launched exclusively or simultaneously in LMIC (23 within 5 years)

A majority of the products will be developed in resource rich settings that do not consider the characteristics (morbidity) of the LMIC where they will be launched

Limited data package when the products are launched in LMIC:
- 'LMIC-only' launch: no experience from HIC for LMIC to rely upon
- 'Simultaneous' launch: trial designs, developer's landscape limit what we know

Launch plan and limited PV capacity multiply risks

**Risk-based assessment**
- Anticipated product pipeline
- Anticipated or potential post-market safety risk
- Pharmacovigilance capacity in launch countries
- Timing of launch

Source: BMGF SSWG Report

**Geographic distribution of product launches, assessed by relative risk (2016-2018)**
WHO-BMGF dialogue: Risk based prioritization of PV activities

- Assess
  - Product launches over 10 years
  - Time frame for product launch
  - Anticipated / potential risks with products
  - Capacity for PV in launch countries

Tailor efforts to identified gaps in target countries
- Protocols & operational guidelines
- End-end vigilance (pre and post approval)
<table>
<thead>
<tr>
<th>National Needs</th>
<th>External Resources</th>
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<tbody>
<tr>
<td>• Awareness and Advocacy</td>
<td>• Lessons learned from RRS</td>
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<tr>
<td>• Capacity and competence</td>
<td>• Information sharing</td>
</tr>
<tr>
<td>• Enablers and infrastructure (guidelines, structures, processes, Resources)</td>
<td>• Fellowships, exchange visits</td>
</tr>
<tr>
<td>• Involve all Stakeholders (public health programmes)</td>
<td>• Consultancies, WHO Collaborating Centres</td>
</tr>
<tr>
<td>• Expand Scope (Dx, Med Errors)</td>
<td>• Technology transfer</td>
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<tr>
<td>• Legal framework</td>
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ADR Reporting ‘App’

• Courtesy Web RADR project
• Negotiated through MHRA
  • Use outside EU, LMIC
• Burkina Faso and Zambia
  • Quick and easy way to report side effects
  • Easier than filling in forms
  • Instant access to medicines safety information
  • It’s free!
Apps Launched
Number of Individual case safety reports (ICSRs) submitted to VigiBase in Sub-Saharan Africa (until May 2017)

- Congo, the Democratic Republic of the Congo: 38,408
- South Africa: 12,614
- Nigeria: 10,801
- Kenya: 10,328

Other countries and their respective numbers of ICSR submissions:
- Botswana: 1,259
- Zambia: 1,012
- Togo: 960
- Angola: 811
- Niger: 736
- Cape Verde: 713
- Burundi: 571
- Mozambique: 259
- Ethiopia: 259
- Senegal: 1215
- Madagascar: 1366
- Tanzania: 1595
- Sierra Leone: 1665
- Namibia: 1771
- Uganda: 2528
- Zimbabwe: 2830
- Ghana: 2861
- Eritrea: 3915
- Kenya: 10,801
- Nigeria: 12,614
- South Africa: 38,408
Quality of Reports in Zambia

![Graph showing the quality of reports in Zambia from 2010 to 2017.]
Quality of Reports in Burkina Faso

![Graph showing the mean completeness score over years from 2010 to 2017. The score starts low in 2010, rises to a peak in 2013, dips slightly in 2014, and then drops gradually to 2017. The x-axis represents the years, and the y-axis represents the mean completeness score.]
What is being reported the most?

Top reported substances in Zambia up until June 2017

- Emtricitabine
- Pyridoxine
- Lamivudine; Nevirapine; Zidovudine
- Enalapril
- Abacavir
- Lopinavir; Ritonavir
- Artemether; Lumefantrine
- Sulfamethoxazole; Trimethoprim
- Lamivudine; Zidovudine
- Lamivudine; Stavudine
- Efavirenz; Emtricitabine; Tenofovir
- Emtricitabine; Tenofovir
- Zidovudine
- Tenofovir
- Co-trimoxazole
- Lamivudine; Nevirapine; Stavudine
- Lamivudine
- Efavirenz
- Nevirapine
- Stavudine

Number of ICSRs in VigiBase
What is being reported the most?

Top reported substances in Burkina Faso up until May 2017

- Pyrimethamine; Sulfadoxine
- Amodiaquine
- Praziquantel
- Sulfamethoxazole; Trimethoprim
- Paracetamol
- Amodiaquine; Artesunate
- Amoxicillin
- Clotrimazole
- Ethambutol
- Isoniazid
- Moxifloxacin
- Pyrazinamide
- Diclofenac
- Protionamide
- Albendazole
- Allopurinol
- Amoxicillin; Pyrimethamine; Sulfadoxine
- Artemether; Lumefantrine
- Quinine
- Amoxicillin
- Amodiaquine; Artesunate
- Paracetamol
- Sulfamethoxazole; Trimethoprim
- Praziquantel
- Amodiaquine
- Pyrimethamine; Sulfadoxine

Number of ICSRs in VigiBase
Sustainability of WEB-RADR’s outputs

WEB-RADR Stakeholder Event
Phil Tregunno, MHRA
Work Completed

- 105 milestones and deliverables completed
- 525.52 person months committed to the project
- 102 Steering Committee actions
- 16 working days left of the project
Opportunities for sustainability

- Data & research
  - Scientific findings
  - Data
  - Recommendations and future research opportunities

- Policy
  - Technology products
  - Legal and ethical framework

- Technology Products
  - App
  - Social media dashboard
Data and research

Research Data
• Commitment to publish data (where possible)
• Including generated reference data sets

Scientific Findings and Future Research
• Published papers being produced across each research area
• Two summary scientific recommendations papers in draft
  • Project findings
  • Future research areas
Policy

**Literature review**
- Data protection in relation to mobile technologies
- Ethical & societal considerations

**Policy recommendations**
- Use of social media for pharmacovigilance
- Use of mobile apps for collection of ADR reports
- Communication considerations
Technology Products

Social media dashboard
• Sustained through policy recommendations
• Many providers of the tools in existence

Mobile apps
• Need to ensure the prototype apps function and evolve beyond the project
• Opportunities to maximise impact for both current adopters and new territories
WEB-RADR Management Board Charter

Role
• Appoint/ review delivery by technology supplier
• Agree cost models for services to be offered
• Set strategic direction for the platform and services offered
• Review and ensure financial position

Founding principles
• Not for profit
• Non-promotional
• Impartial
• Sustainable
Proposed Management Board
Mobile Platform Technology Provider

• Guard against defects associated with technology change
• Maintain and develop the platform to enhance and expand use
• Facilitate roll out platform to more countries
• Opportunity to repurpose technologies in new settings to increase impact

✓ Supplier appointed through procurement framework
✓ Proven success in delivery of commercial multi-brand, multi-site app and platform delivery
✓ Multi-national, multi-currency mobile commerce application including ‘live’ branding for rapid roll out to new partners
Exploitation Call

Background

• Intention of the call is for IMI1 projects to maximise the impact of their deliverables under the IMI2 framework
• WEB-RADR proposed in 2016 that the mobile app platform should be considered in this call
• Currently preparing a proposal to be considered alongside other projects

WEB-RADR Proposal

• Mobile app platform enhancement and technology adoption
  • New territories
  • Diversification of adopters
• Platform interoperability with the healthcare network
  • Facilitated by a terminology mapping work stream
Table discussion

• What aspects of the WEB-RADR mobile platform might be exploitable in your organisation in future?
• How could the platform be extended to become more useful to you?
• What would be a measure of impact of the mobile app
• Should / can the platform be exploited outside the EU?